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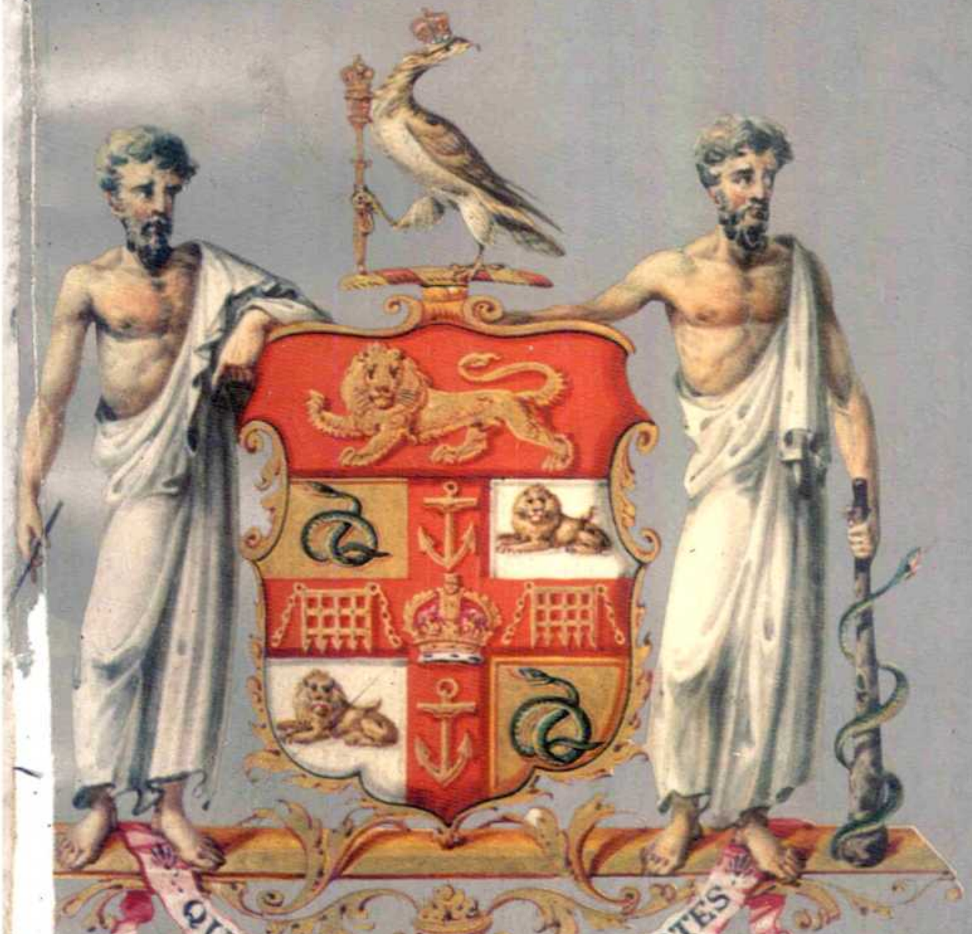

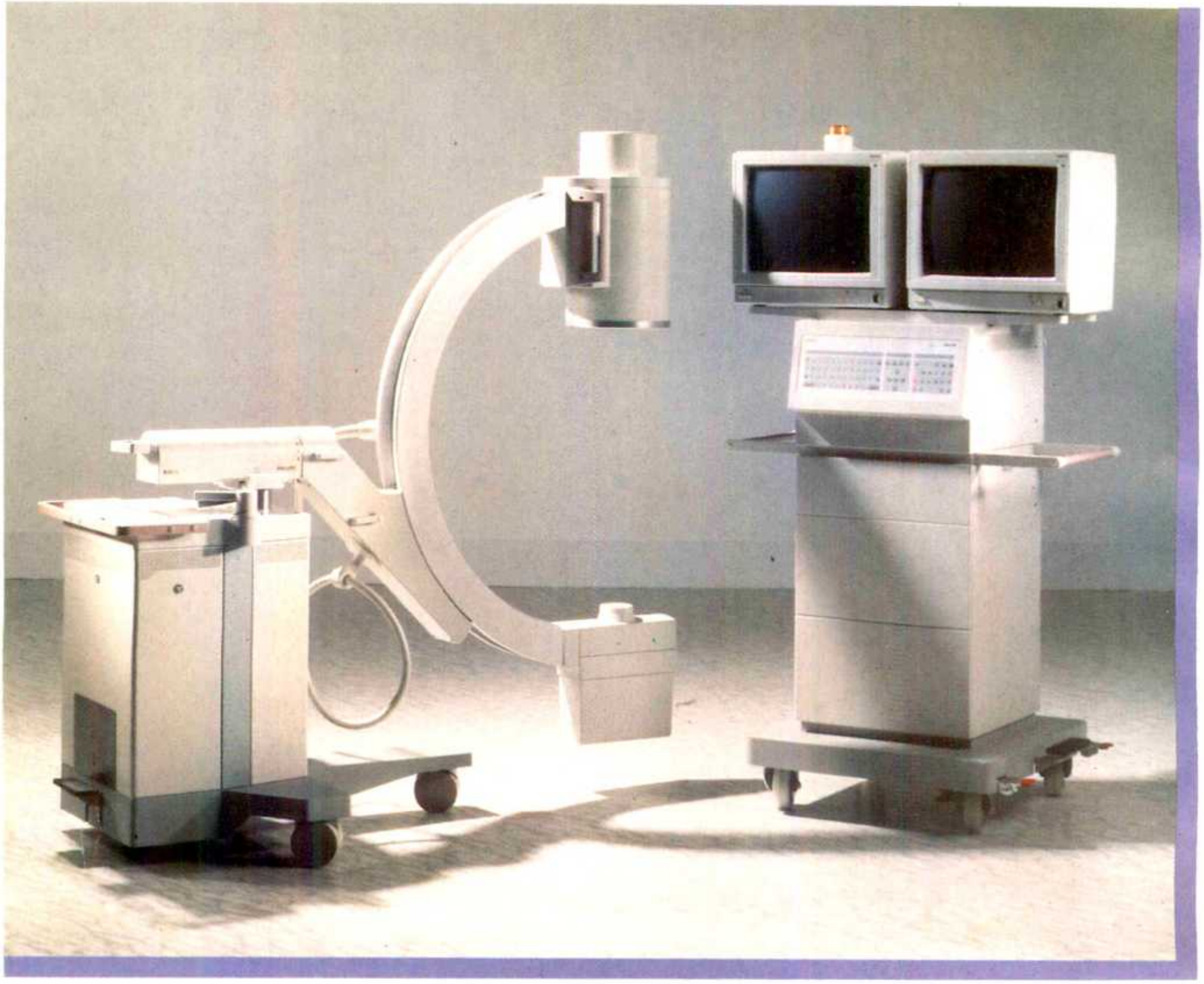

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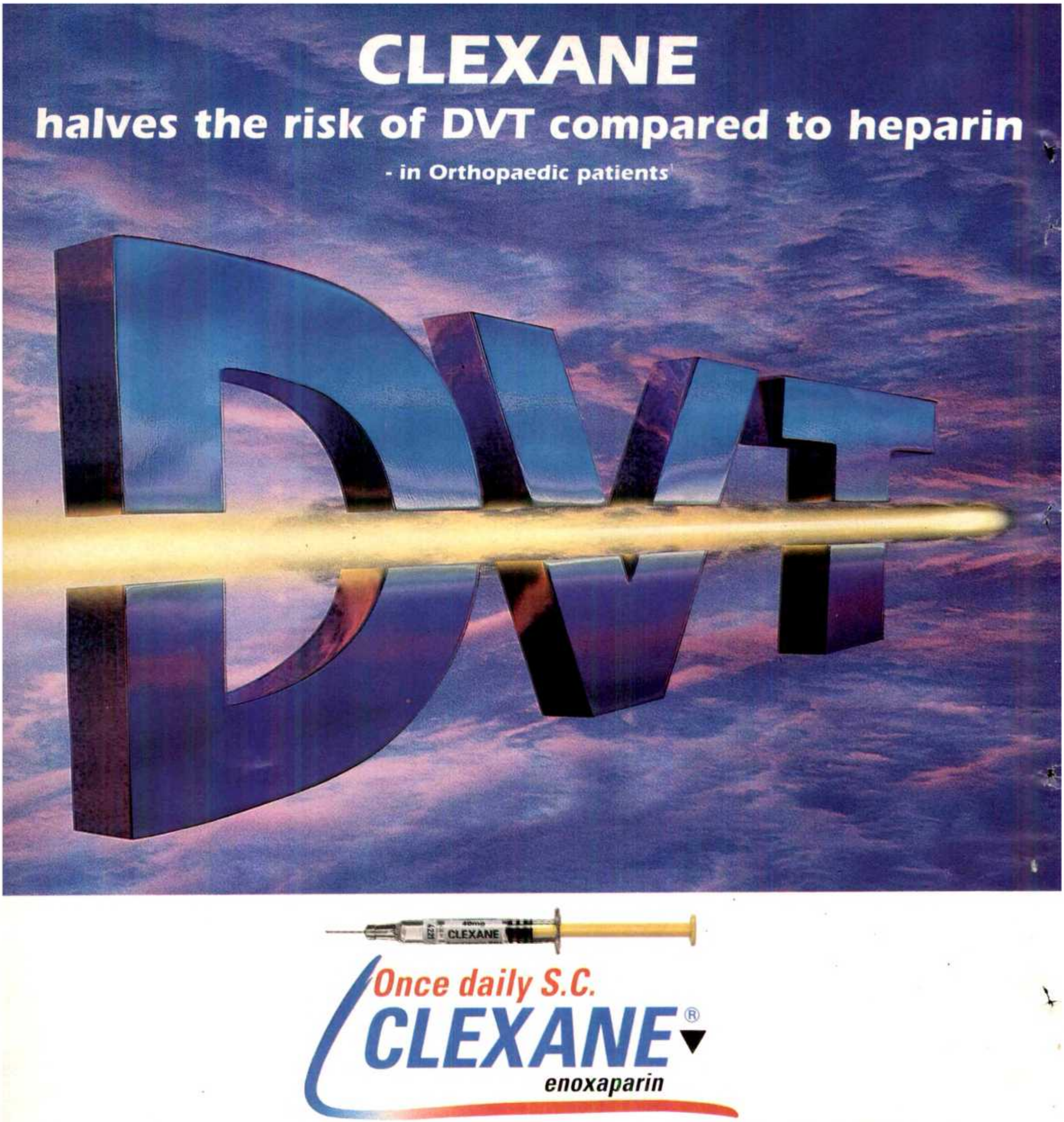
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1. Planes A *et al.* Thrombosis and Haemostasis 1988; **60** (3): 407-410.

Br. J. Surg. 1991, Vol. 78, May, 513–515

Bleeding oesophageal varices and the surgeon

Endoscopic injection sclerotherapy for oesophageal varices, first described 50 years ago, became fully accepted in clinical practice in the 1970s, following the introduction of the flexible endoscope. With an apparent control rate of 80–90 per cent in acute variceal haemorrhage it seemed that the entire management of portal hypertension and bleeding oesophageal varices had fallen into the hands of the endoscopist and that the surgeon, unless himself an endoscopist, had little part to play.

The pendulum, however, had swung too far. While the benefits of sclerotherapy in acute haemorrhage are undoubted, its effectiveness is not as great as the 80–90 per cent often reported. In two-thirds of patients admitted with acute haemorrhage, bleeding has ceased at the time of endoscopy, either spontaneously or in response to initial treatment such as the use of vasoactive drugs. Nevertheless, injection sclerotherapy does prevent recurrent bleeding during the hospital admission and has become the 'gold standard' by which all other treatments for the emergency control of variceal haemorrhage must be compared.

The efficacy of injection sclerotherapy is less clear in other aspects of management. It is necessary to appreciate that there are three separate clinical scenarios in variceal management: *emergency* treatment to stem haemorrhage; *secondary prophylaxis* to prevent later rebleeding; and *primary prophylaxis* to prevent bleeding from varices which have not yet bled. Does surgery have a role in any of these areas?

In acute variceal haemorrhage, as in other forms of gastrointestinal haemorrhage, operation is not primarily indicated. Although Orloff has vigorously championed emergency operation for many years[1], few consider that portasystemic shunting should be the first line of treatment. The mortality rate can be high (50 per cent in those with severe liver disease and 20 per cent overall), and the operation may be unnecessary because bleeding may already have ceased. Nevertheless, Orloff may have had a point and an important study from San Francisco[2] has demonstrated that portacaval shunts were more effective than injection sclerotherapy in preventing early recurrence of bleeding.

What about other operations in the emergency control of haemorrhage? Apart from Japan where the Sugiura operation (splenectomy, paraoesophageal devascularization and oesophageal transection) remains popular, major oesophageal and gastric operations have been largely replaced by oesophageal stapling transection alone. Few would advocate oesophageal transection as the initial treatment to stop bleeding but its relative safety means that it should be employed expeditiously when initial measures fail. Thus, two abortive attempts to control bleeding with, say, sclerotherapy should lead to oesphageal transection, provided that oesophageal varices are the source of recurrent haemorrhage. Procastination and persistence with tamponade, vasoactive drugs and sclerotherpy should be avoided, because death from liver failure becomes inevitable even if bleeding is controlled ultimately by transection[3]. Nevertheless, it must be appreciated that transection is a temporizing procedure and that varices may reform within a few months, although they can be controlled by sclerotherapy.

The source of haemorrhage after apparently successful injection sclerotherapy may be gastric varices, which are difficult to treat endoscopically, especially when they lie in the fundus. If operation is needed, the simplest procedure is transgastric plication of the varices which may be combined with oesophageal stapling. My own experience suggests that this operation is of value only where bleeding occurs from varices which radiate from the gastro-oesophageal junction. Bleeding from gastric varices in the greater curvature of the stomach, often associated with marked splenomegaly, is more difficult to control. Under these circumstances splenectomy, although rather bloody, is effective. If neither procedure is technically possible, or is ineffective, the surgeon must be prepared to carry out an emergency portasystemic shunt.

Prevention of late rebleeding (i.e. secondary prophylaxis) remains the major unsolved problem in portal hypertension. Recent experience suggests that the initial wave of enthusiasm for endoscopic sclerotherapy was not fully justified. The benefits of long-term sclerotherapy appear to spring from effective control of separate acute

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bleeding episodes, rather than from variceal obliteration. There is little evidence that sclerotherapy improves survival and, indeed, this has clearly been demonstrated only in one trial[4]. This is hardly surprising given that varices and portal hypertension indicate advanced liver disease. If, in the medium term, endoscopic sclerotherapy does not reduce the number of bleeding episodes, operation must be considered.

What then is the role of surgery in secondary prophylaxis? The main indication for portasystemic shunts is still the prevention of recurrent bleeding. Total shunts (e.g. end-to-side portacaval, mesocaval) can prevent haemorrhage but, presumably because they reduce liver blood flow, they are followed by portal systemic encephalopathy in about 20% of patients. Benefit in the form of survival is not markedly significant. Of the selective shunts the best known is the distal splenorenal (Warren) shunt which selectively decompresses the oesophagogastric varices through the splenic–renal vein anastomosis but maintains liver perfusion in the hope that hepatoportal encephalopathy will be avoided. The results, however, have been mixed[5–7]. Although Warren's group reported a low mortality (9 per cent) and low incidence of postoperative encephalopathy, larger randomized trials comparing total and selective shunts have shown rates of mortality and long-term encephalopathy which are remarkably similar. However, most surgeons experienced in this field hold that the distal splenorenal shunt offers better results, in terms of quality of life. It is technically more demanding and is contra-indicated in the presence of intractable ascites. It has the advantage that the upper abdomen is not transgressed and is therefore the operation of choice in patients who may have to have subsequent hepatic transplantation. The role of other selective shunts, such as the narrow bore portacaval H-graft shunt, has still to be established by good randomized controlled trials.

Surgery and endoscopic sclerotherapy should not be regarded as competing approaches; indeed, their roles may be complementary. Shunt operations should be considered earlier, rather than later in the treatment protocol, in those patients in whom endoscopic sclerotherapy has failed. Warren *et al.*[8] and Paquet *et al.*[9] have claimed better results with such a strategy compared to sclerotherapy alone.

None of the treatments so far discussed reverses the underlying liver disease, inexorable progress of which accounts for their failure to influence long-term survival. Hepatic transplantation is advocated increasingly in the management of portal hypertension and oesophageal varices. The results in cirrhotic patients are reasonably good, with a 4-year survival rate of 73 per cent in Grade C cirrhotics compared with 32 per cent after shunting and 59 per cent with sclerotherapy[10]. In patients with primary biliary cirrhosis, hepatic transplantation should be considered soon after diagnosis. However, the majority of cirrhotics in the United Kingdom are alcoholic and, until the role of hepatic transplantation in these patients is clarified, we can probably do no better than adhere to the policy advocated by Bismuth and his group[10]. Patients who present with variceal haemorrhage should be controlled initially with endoscopic sclerotherapy. In those with severe hepatic impairment, liver transplantation should be considered and if surgical intervention is required before it can be carried out, nothing should be done to make transplantation more difficult. Oesophageal transection and end-to-side portacaval shunt may frustrate future access to the right upper quadrant of the abdomen. A distal splenorenal shunt, on the other hand, decompresses the liver without excessively compromising the field for future hepatic transplantation. In young and non-alcoholic cirrhotics who have good liver function, a portasystemic shunt (probably a distal splenorenal or an H-graft shunt) may be the optimal treatment. In those in whom the liver disease is of intermediate severity (Child group B), treatment should be determined on an individual basis.

There is one scenario, however, in which surgery does *not* have a role, namely in primary prophylaxis to prevent haemorrhage in a patient, usually cirrhotic, in whom oesophageal varices have been detected, but have not yet bled. The evidence from several controlled trials is that, although bleeding may be prevented, survival is not enhanced. Primary prophylaxis by any means has not been a rewarding endeavour.

Thus the role of the surgeon in the treatment of portal hypertension and bleeding oesophageal varices is expanding once more. With increasing disenchantment with long-term endoscopic sclerotherapy, other forms of treatment are necessary and it is likely that selective shunt operations and hepatic transplantation will have an assured place in the near future.

Professor Sir Robert Shields

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1. Orloff MJ, Bell RH, Greenburgh AG. Prospective randomised trial of emergency portacaval shunt and medical therapy in unselected cirrhotic patients with bleeding varices. *Gastroenterology* 1986; **90**: 1974.
2. Cello JP, Grendell JH, Crass RA *et al.* Endoscopic sclerotherapy versus portacaval shunt in patients with severe cirrhosis and acute variceal hemorrhage. Long-term follow up. *New Engl J Med* 1987; **316**: 11–15.
3. Jenkins SA, Shields R. Variceal haemorrhage after failed injection sclerotherapy: the role of emergency oesophageal transection. *Br J Surg* 1989; **76**: 49–51.
4. Westaby D, MacDougall BR, Williams R. Improved survival following injection sclerotherapy for esophageal varices: final analysis of a controlled trial. *Hepatology* 1985; **5**: 827–30.
5. Milliken W Jr, Warren WD, Henderson JM *et al.* The Emory prospective randomized trial: selective versus non-selective shunt to control variceal bleeding. Ten-year follow-up. *Ann Surg* 1985; **201**: 712–22.
6. Grace ND, Conn HO, Resnick RH *et al.* Distal splenorenal vs portal-systemic shunts after hemorrhage from varices: a randomized controlled trial. *Hepatology* 1988, **8**: 1475–81.
7. Spine GP, Galeotti F, Opocher E *et al.* Selective distal splenorenal shunt versus side-to-side portacaval shunt. Clinical results of a prospective, controlled study. *Am J Surg* 1988; **155**: 564–71.
8. Warren WD, Henderson JM, Milliken W Jr *et al.* Distal spleno-renal shunt versus endoscopic sclerotherapy for long-term management of variceal bleeding. Preliminary report of a prospective randomized trial. *Ann Surg* 1986; **203**: 454–62.
9. Paquet K-J, Mercado MA, Gad HA. Surgical procedures for bleeding esophageal varices when sclerotherapy fails: a prospective study. *Am J Surg* 1990; **160**: 43–7.
10. Bismuth H, Adam R, Mathur S, Sherlock D. Options for elective treatment of portal hypertension in cirrhotic patients in the transplantation era. *Am J Surg* 1990; **160**: 105–10.

Br. J. Surg. 1991, Vol. 78, May, 516–517

Safe surgery in sickle cell disease

Sickle cell disease due to homozygous inheritance of the haemoglobin variant HbS is one of the commonest genetic disorders world-wide. An estimated 70 million people carry the sickle gene. Though the majority are of Afro-Caribbean origin, sickle cell disease is also prevalent in parts of the Mediterranean, Middle East and India, its frequency and geographic distribution reflecting selective resistance among heterozygotes to *Plasmodium falciparum* malaria. Sickling syndromes also occur in individuals who coinherit HbS and other β-globin variants such as HbC or β-thalassaemia. The pathological manifestations of sickle cell disease are due to the altered physical properties of HbS. On deoxygenation HbS undergoes polymerization causing red cell distortion and rigidity. The reduced lifespan and inability to traverse the microvasculature of sickled red cells are responsible for haemolytic anaemia and vaso-occlusive 'crises', the hallmarks of sickle cell disease[1].

Among the protean manifestations of sickle cell disease are several for which surgery may be required. These include gallstones (detectable by ultrasonography in up to 40 per cent of cases by the age of 18 years), osteomyelitis, avascular necrosis of the femoral head, splenic sequestration, priapism, proliferative retinopathy, end-stage renal disease and chronic leg ulcers[2–7]. Surgery in the sickle cell patient carries a potentially high morbidity rate[8]. Perioperative pulmonary complications, particularly acute chest syndrome, may be life-threatening and necessitate prolonged hospitalization. While these problems are encountered mainly in inner cities with large ethnic minority populations, greater population mobility makes their recognition of wider importance in surgical practice.

Most patients with sickle cell disease are aware of the diagnosis and some centres in the UK issue a haemoglobinopathy card giving details of the haemoglobin genotype. It is important to remember that anaemia is not universal in sickling disorders. All patients at risk on the grounds of ethnic origin should therefore be screened prior to elective or emergency surgery. This is conveniently achieved by cellulose acetate haemoglobin electrophoresis which detects HbS and other variants with distinct electrophoretic mobilities. The disease state is easily distinguished from sickle cell trait which, in the absence of severe hypoxia, carries little increased operative risk with modern anaesthetic techniques. Commercial kits (e.g. Sickledex, Ortho, High Wycombe, UK), which demonstrate HbS by virtue of its insolubility in the presence of a reducing agent, do not differentiate between disease and trait and should be reserved for emergency out-of-hours use. The Hb genotype should be confirmed at the earliest opportunity by electrophoresis.

Specific measures may be adopted to minimize the risks of surgery in sickle cell disease. In patients requiring surgery under general anaesthesia precautions against hypoxia, dehydration and acidosis, all of which may trigger sickling, are important. These include preoxygenation, a fraction of inspired oxygen ($F_{\mathrm{i}O_2}$) of at least 0.5, and adequate intravenous fluids (≥ 3 litres per m^2 per 24 hours) to counter hyposthenuria induced by repeated sickling involving the vasa recta. Anaesthetic techniques which minimize fall in cardiac output and hence venous desaturation are preferable. Body temperature should be maintained to avoid reflex vasoconstriction and intravenous fluids given via a blood warmer. High-flow perfusion during extracorporeal circulation has been used in cardiac by-pass surgery to avoid the need for cooling[9]. If intraoperative transfusion is required this should be given judiciously maintaining a haematocrit of <45 per cent to avoid increasing blood viscosity. Operations requiring a bloodless field carry a potentially high risk of inducing sickling[10]. Where the use of tourniquets is essential, the limb should be thoroughly exsanguinated and ischaemia time kept to a minimum.

While it is generally considered desirable to reduce HbS levels prior to surgery, there is no clear consensus regarding the optimal transfusion regimen and levels required for different surgical procedures. These questions are currently the subject of a prospective randomized multi-centre study in the United States[11]. Preoperative transfusion to reduce HbS levels is advocated by most centres in the UK. By contrast, in the tropics, where the scale of the problem is greater, surgical practice may be governed by the availability of safe blood products. The benefits of transfusion have to be weighed against the attendant risks, particularly red cell alloimmunization which occurs in up to 20 per cent of transfused sickle cell patients[12], and transmission of hepatitis and other blood-borne infections. At King's College Hospital we routinely

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undertake preoperative transfusion to achieve an HbS level of <30 per cent in all cases undergoing thoracic, abdominal, neurosurgical or major orthopaedic procedures and any surgery in patients with pre-existing cardiac or respiratory disease. Transfusion may be unnecessary for minor operations, including some dental, gynaecological and ENT procedures. Where doubt exists simple transfusion aiming at a haemoglobin level of 10 g/dl may suffice. For elective surgery the HbS level can be reduced by hypertransfusion to attain a haemoglobin level above steady state values, thereby suppressing endogenous erythropoiesis. However this requires multiple transfusions over a period of several months. More rapid results can be obtained by exchange transfusion and this is the preferred option for emergency surgery. Automated continuous cell separators allow complete red cell exchange within hours but are available in only a few specialized centres.

Adopting these guidelines we have observed very few sickle-related complications in over 200 operations under general anaesthesia performed since 1970 at King's College Hospital. However, it should be remembered that while these measures provide a useful framework, close liaison between surgeon, anaesthetist and haematologist remains the cornerstone of successful surgery in the sickle cell patient.

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1. Serjeant GR. Sickle Cell Disease. Oxford: Oxford University Press, 1985.
2. Bond LR, Hatty SR, Horn ME, Dick M, Meure HB, Bellingham AJ. Gallstones in sickle cell disease in the United Kingdom. *Br Med J* 1987; **295**: 234–6.
3. Clarke HJ, Jinnah RH, Brooker AF, Michaelson AD. Total replacement of the hip for avascular necrosis in sickle cell disease. *J Bone Joint Surg* [*Br*] 1989; **71**: 465–70.
4. Pappis CH, Galanakis S, Moussatos G, Keramidas D, Kattamis C. Experience of splenectomy and cholecystectomy in children with hemolytic anaemia. *J Pediatr Surg* 1989; **24**: 543–6.
5. Dewan PA, Tan HL, Auldist AW, Moss DI. Priapism in childhood. *Br J Urol* 1989; **64**: 541–5.
6. Jampol LM. Vitrectomy surgery in proliferative sickle cell retinopathy. *Am J Ophthalmol* 1987; **104**: 553–4.
7. Donnelly PK, Edmunds ME, O'Reilly K. Renal transplantation in sickle cell disease. *Lancet* 1988; **23**: 229.
8. Bentley PG, Howard ER. Surgery in children with homozygous sickle cell anaemia. *Ann R Coll Surg Engl* 1979; **61**: 55–8.
9. Bomfim V, Ribeiro A, Gouvea F, Pereira J, Bjork V. Sickle cell anemia and mitral valve replacement. Case report. *Scand J Thorac Cardiovasc Surg* 1989; **23**: 75–7.
10. Martin WJ, Green DR, Dougherty N, Morgan D, O'Heir D, Zarro M. Tourniquet use in sickle cell disease patients. *J Am Pediatr Assoc* 1984; **16**: 291–4.
11. National SCA Preoperative Transfusion Study Group. Preoperative transfusion (TX) in sickle cell anemia. *Blood* 1989; **74**(Suppl 1): Abstract.
12. Davies SC, McWilliams AC, Hewitt PE, Devenish A, Brozovic M. Red cell alloimmunization in sickle cell disease. *Br J Haematol* 1986; **3**: 29–44.

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Role of interstitial therapy in the treatment of liver cancer

Conventional palliative management of inoperable focal hepatic tumours remains unsatisfactory. Interstitial techniques such as cryotherapy, alcohol injection, low power laser hyperthermia and interstitial radiotherapy offer alternative approaches. Cryotherapy is an effective and precise technique for inducing tumour necrosis. It can only be performed at laparotomy making it relatively invasive and retreatment impractical. Alcohol is cheap and can be injected percutaneously. However, inhomogeneous distribution produces imprecise and non-reproducible lesions. Low power laser hyperthermia produces precise and reproducible areas of necrosis that are roughly spherical in shape. At present, this technique is most effective for small tumours. Interstitial radiotherapy remains the least evaluated of all the interstitial techniques. Unlike cryotherapy and low power laser hyperthermia, the biological effect of ethanol injection and interstitial radiotherapy cannot be monitored in real time by ultrasound. With the exception of cryotherapy, all methods can be applied percutaneously with low morbidity and mortality. None of these techniques is established, but they may offer the prospect of cure in cases where all areas of tumour can be positively identified and fully treated. However, in most instances the intention is to control the growth of relatively small discrete volumes of tumour within the hepatic parenchyma.

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The recent leading article by Bengmark on the palliative management of hepatic tumours highlighted the inadequacies of existing treatment modalities[1]. Bengmark's concluding comments were "... attempts should be made to develop a palliative treatment for patients with liver tumours which is simple, can be performed on an ambulatory basis for life, involves active participation by the patient, and which has minimal or no side-effects. Such treatment should not reduce mental and physical activity. At present the goal should be growth control and not cure". We submit that interstitial treatment methods go some way to fulfilling these criteria. Such techniques are currently the focus of active research.

Interstitial therapy may be defined as any method of treatment where the therapeutic stimulus is delivered directly to a selected site of intended tissue damage, even if this is in the centre of a solid organ, with preservation of the surrounding normal tissue. In the context of cancer therapy, this implies that the noxious agent is delivered intratumorally, therefore achieving localized damage of pathological tissue. The focal nature of tumour necrosis produced using interstitial therapy makes it unsuitable for dealing with diffuse malignant disease of the liver. The rationale for the use of interstitial techniques is based on the premise that by reducing the volume of viable tumour or preventing further tumour growth, one may lengthen survival. Interstitial techniques can be divided into methods which produce cell death by: (1) hyperthermia as achieved by radiofrequency, microwave, ultrasound and laser modalities, (2) cryotherapy, (3) chemical means such as alcohol, and (4) ionizing radiation.

We have reviewed the available literature on interstitial treatment methods to assess the efficacy, safety, ease of application and costs of each.

Background

Although primary malignant disease of the liver is rare in the UK (in contrast to its high incidence in Africa and much of Asia), about a third of all patients with cancer will have liver metastases before death. Most of these patients have multifocal or diffuse hepatic disease, although a proportion appear to have just a small number of discrete areas of tumour within the liver with no evidence of extrahepatic disease once the primary has been removed. This includes about 5-10 per cent of patients with liver metastases from colorectal cancer and 9-17 per cent of all patients with hepatocellular carcinoma[2-4]. In major series of liver resection for colorectal metastases published in the last decade, the perioperative mortality rate ranges from 4 to 12 per cent[5-8] with 12-25 per cent of patients suffering a major complication[5,9]. However, even in the best circumstances, it is a major procedure with a prolonged recovery period, and many patients later develop recurrent disease in the liver or elsewhere. Despite this, 5-year survival rates ranging from 20 to 40 per cent are quoted[6,7,10]. Alternative forms of therapy such as hepatic dearterialization, hepatic artery ligation, embolization, external beam irradiation and chemotherapy are recognized palliative procedures which are simpler than hepatic resection although they still carry some morbidity and mortality without convincing improvement in survival[1,11].

Hyperthermia

The concept of treating tumours by heat is ancient, with the earliest reference to its use found in *The Edwin Smith Surgical Papyrus* which has been carbon dated to 1700 BC[12]. The

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haemostatic and tissue destroying properties of heat were also used widely by the Greeks and Romans[13].

The attractions of the use of hyperthermia to destroy tumours were based on early reports of increased heat sensitivity of neoplastic cells compared to their normal counterparts. However, there seems to be little consistent difference between the response of normal and neoplastic cells to thermal insult except possibly at low pH[14]. Thus, to be of any value in the treatment of liver tumours, hyperthermia must be applied focally to avoid widespread damage to normal cells. If this can be done, it has the added advantage that there is no cumulative toxicity, making retreatment of relapse possible. The first discussion on the use of regional hyperthermia on the liver came after reports of hepatic damage in 1943 by King *et al.* and Wallace *et al.* in patients treated by whole body hyperthermia for resistant gonococcal and non-specific urethritis[15,16]. This was attributed directly to the effects of raised body core temperature and emphasizes the inherent sensitivity of the liver to heat.

Radiofrequency and microwave techniques

Regional hyperthermia may be induced by radiofrequency or microwave techniques using non-invasive and invasive applicators[17]. The applicators are the weakest but most vital component of the inductive system. The energy from external applicators must pass through normal tissue before reaching the target area and no system currently available can achieve the precision of heat delivery possible with invasive techniques[18]. Invasive radiofrequency and microwave applicators have to be implanted within tumour tissue in the liver. This approach is impractical for multiple and deeply located tumours[17].

Ultrasound

Non-invasive ultrasound probes used as a thermal source are both directional and focusable and thus have the potential for accurate heat deposition in a given site[18]. Experimental work[19] has shown that by using multiple transducers it is possible to produce uniform steady state temperatures up to 10°C above body temperature in an area 6 cm in diameter and to a maximum depth of 10 cm. However, invasive therapeutic ultrasound probes are not practical for organs like the liver.

Lasers

The attraction of lasers for interstitial therapy is that the laser light can be transmitted easily down thin flexible fibres (0·2–0·6 mm diameter) and is only emitted from the distal tip of the fibre. The type used most commonly in gastroenterology is the Neodymium Yttrium Aluminium Garnet laser (Nd:YAG). It emits light at a wavelength of 1064 nm (near infrared) which penetrates tissue well. The concept of interstitial laser hyperthermia is simple[20] and was first described in 1983. The technique depends on insertion of a laser fibre into a tumour within a solid organ. The laser is activated at low powers (0·5–5·0 watts) with long exposure times (500–1000 s). The biological response depends on the wavelength, light intensity and absorption characteristics of the tissue. Selectivity is achieved by the localization of heat deposition to the tumour, rather than by any difference in response between normal and neoplastic areas. There is therefore little or no damage to the surrounding tissues other than the small track required to pass the fibre. Experimentally, single fibre treatment sites can produce areas of necrosis up to 1·5 cm in diameter and, with four fibres activated simultaneously, this can be increased to 4 cm. The lesions produced are well defined, predictable and roughly spherical in shape around each fibre[21,22]. They can be well delineated in real time by ultrasound and there is good correlation between the extent of the evolved lesion seen sonographically and the final extent of the zone of necrosis at necropsy 5–7 days after treatment. The key to safe and effective clinical application of the technique is to match the area of thermal damage to the extent of the tumour and to ensure subsequent safe healing which in the case of the liver is achieved by regeneration and fibrosis. At all stages of the healing process the structural and functional integrity of the surrounding normal tissue must be retained. Because the laser fibre is buried within the tissue it is not possible to assess the ensuing and final tissue changes by inspection, so one is dependent on a monitoring method. Ultrasound, computed tomography, magnetic resonance imaging and angiography can all fulfil such a role.

The first reported clinical work on interstitial laser hyperthermia for liver tumours came from Hashimoto *et al.* in Japan[23]. At laparotomy, a quartz fibre tip was inserted into the tumour under intraoperative ultrasound guidance. A Nd:YAG laser at an output of 5 watts was activated until 1000 joules of energy had been delivered per cubic cm of tumour. Two primary hepatocellular cancers measuring 3 and 5 cm in diameter were treated. The α-fetoprotein levels decreased to normal levels within 3 months of treatment. A further eight cases of metastatic liver cancer of colorectal origin were similarly treated and all showed a dramatic fall in carcinoembryonic antigen (CEA) levels. There were no procedure-related complications but no comment was made on the influence of treatment on patient survival. Schroder *et al.*[24] in Finland treated four patients with advanced malignant disease of the liver using a similar approach to Hashimoto *et al.*[24]. Computed tomographic follow-up at 1 and 2 weeks showed areas of necrosis at the treatment sites. However, one patient developed an infection in a necrotic area and another died from an air embolus where coaxial gas was used to cool the sapphire tip on the fibre.

The need for laparotomy as described in the latter two papers makes interstitial laser hyperthermia a relatively invasive procedure. However, in a pilot study carried out in London, a percutaneous approach with ultrasound guidance for positioning the laser fibres was used. Eight patients with a total of 13 hepatic metastases and no extrahepatic spread have been treated. The average tumour diameter was 3 cm with a range of 1.5 to 6.0 cm. The mean follow-up time was 5 months. The primary tumour site was the colon and rectum in six patients and the breast and stomach in the remainder. All patients had a pretreatment hepatic computed tomographic and ultrasound scans; none had more than four hepatic metastases.

After a combination of intravenous sedation and antibiotics, one or more hollow 19-gauge needles up to a maximum of four, each bearing a laser fibre, were inserted percutaneously under ultrasonographic control into the selected metastasis. Each fibre emitted a power of 1·5–2·0 watts from a Nd:YAG laser which was maintained for 500 s. The ensuing thermal changes were monitored in real time by ultrasound. There were no early or late complications and all patients left hospital within 24 h of treatment. Real time ultrasound monitoring revealed that the treated metastasis is converted from a mixed echogenic to a hyperechogenic pattern. Follow-up hepatic computed tomographic scans performed at 6–8 weeks revealed that six of 13 metastases (five of six were $\leqslant 2$ cm in diameter) showed necrosis in $\geqslant 50$ per cent of their respective volumes with a further two metastases having necrosis of $\leqslant 25$ per cent of their volumes. However, five metastases showed no obvious necrosis (four of five were $\geqslant 4$ cm in diameter) of which two had increased in diameter. Disseminated disease has since become apparent in two patients.

The percutaneous approach using interstitial laser hyperthermia seems the simplest of the thermal treatments. It can be performed by an interventional radiologist with the minimum of nursing staff and short hospitalization times. As with all percutaneous techniques, not all parts of the liver are readily available to percutaneous access, e.g. deep high lesions in the right lobe. The initial cost of purchasing a suitable lasers high (£50 000) but if the technique becomes established, the range of tumours that might be treated by this technique is considerable and could include lesions of the pancreas, breast, thyroid and indeed any solid organ accessible to fibre insertion. The same instrument can be used for a range of other applications, particularly endoscopic techniques in gastroenterology, thoracic medicine, urology and gynaecology[25,26]. Nevertheless, interstitial laser hyperthermia is still at the stage of pilot clinical studies.

Cryotherapy

Cryoablation, the application of a cooling agent to biological tissue with the intention of inducing tissue necrosis, has been reported sporadically since the middle of the last century although advances have been hampered by technical problems[27–33]. Improvements in probe design and imaging technology now mean that superficial and deeply seated lesions within the liver can be treated with real time intraoperative ultrasound monitoring. There is good correlation between the extent of the frozen area seen at the end of treatment and the final extent of the necrotic zone produced[34]. The evolving and final area of frozen tissue can be seen sonographically in real time as an iceball generated around the cryoprobe[35].

Several factors operate when a cryogenic stimulus is applied to biological tissue leading to irreversible cell damage. These include cellular dehydration and denaturing of structural and functional proteins. A more remote effect has been reported experimentally: namely the induction of an immunological response to residual viable tumour[36]. This is thought to be a result of the liberation of tumour-specific antigens which provoke a host immune reaction, although it is not clear whether this could have any clinical relevance.

Zhou *et al.* reported on 27 of 60 patients with primary hepatocellular carcinoma treated with cryotherapy alone[34]. Twenty-one of the 60 patients had lesions <5 cm but what proportion of these made up the 'cryotherapy only' treatment group is not disclosed. Patients were treated at laparotomy using a 3–5 cm diameter hollow plate probe that circulated liquid nitrogen through an insulated metal sheath with temporary occlusion of the hepatic blood supply. Assessment of treatment was made visually and by thermocouples placed around the treated lesion. There were no procedure-related complications. The survival rates in the 27 cases treated with cryosurgey alone were 33 per cent, 23 per cent and 4 per cent at 1-year, 2-year and 5-year respectively. These results could almost certainly be improved because thermocouple and visual assessment make no consideration for depth and margin of the freezing front and therefore tumour eradication is likely to have been incomplete in at least some of these cases. Cryotherapy plus synchronous or metachronous resection of the frozen area was performed in five patients. Histological evaluation showed only scar tissue at the sites where the tumour had been treated before resection.

Unlike Zhou *et al.* who treated superficial lesions only, Ravikumar *et al.* treated ten patients with multiple deeply located metastatic lesions within the liver using liquid nitrogen at −196°C with 8 mm and 12 mm diameter interstitial probes under intraoperative ultrasound guidance[35]. The first five patients in the series underwent synchronous resection of the treated frozen area. The subsequent five patients were treated in a similar manner but three freeze cycles were used for each lesion and the treated area was left *in situ*. The largest iceball generated was 3 cm but there is no mention of the size or number of the lesions treated. Follow-up ranged from 4 to 17 months (median of 7·5 months) and consisted of tumour imaging and serial assays of serum tumour markers. Those patients with elevated CEA levels and no gross residual disease following treatment showed a progressive fall in CEA levels over several months. Serial computed tomographic scans showed evidence of tumour necrosis and diminution in size of all treated lesions. Surprisingly, of six patients who had lesions cryoablated and then resected (five synchronously and one metachronously) a comment is only made in one patient to the effect that of two lesions treated and resected, one showed evidence of viable tumour.

A further report on cryosurgery for metastatic liver disease has come from Charnley *et al.*[37]. Seven patients with a total of 39 metastases having a range of diameters of 0·5 cm to 6·5 cm were treated at laparotomy using liquid nitrogen with a 5 mm interstitial probe under intraoperative ultrasound guidance. All patients were discharged 7–10 days after surgery. Follow-up time ranged from 1 to 6 months. Computed tomographic scanning of all treated lesions showed evidence of tumour necrosis and regression in size at 6 weeks. CEA levels fell in three patients and one patient with carcinoid syndrome became asymptomatic.

Undoubtedly, modern technology has allowed cryotherapy to evolve as a feasible and safe technique for treating focal hepatic tumour deposits. The main disadvantage is that patients have to undergo laparotomy with its associated morbidity. Operation times may become unacceptably long when dealing with several lesions and vascular adhesions around previous treatment sites may make retreatment of recurrent disease difficult. A possible advantage of the surgical approach is that at laparotomy it is possible to mobilize the liver fully and provide access to all parts of the liver for treatment, an advantage not enjoyed by percutaneous techniques. Another benefit is that intraoperative ultrasonography provides superior resolution when compared with conventional ultrasound. Small lesions <2 cm in diameter which might otherwise be missed can therefore be treated. However, despite relatively inexpensive equipment (£5000), further costs are incurred in hospitalization, operating and theatre time, with their associated demand on surgical, anaesthetic and nursing manpower.

Alcohol therapy

The use of alcohol to destroy biological tissue is well established in medicine as, for example, in coeliac ganglion blocks[38]. Shinagawa *et al.*[39] and Fujimoto *et al.*[40] independently reported their attempts at ultrasound guided percutaneous alcohol injection for intrahepatic neoplasms in the mid 1980s. Improvements in the resolution capability of ultrasonography coupled with the low costs, ease of handling and ready availability of alcohol have allowed the emergence of hepatic intratumoral injection of alcohol as a viable alternative in the palliative management of liver cancer.

Livraghi *et al.*, keen advocates of alcohol therapy, have published their results in two series[41,42]. A total of 37 lesions <4·5 cm in diameter in 28 patients were treated by percutaneous alcohol injection under sonographic control. In 33, the lesions were primary hepatocellular carcinomas, the remainder being metastatic liver tumours. The number of injections per lesion varied from three to 24 depending on the initial diameter and assessment between injection sessions. Assessment included fine needle biopsy and ultrasonography after every three injections with a maximum of nine injections in the first 11 patients, and fine needle biopsy and computed tomographic scan after every six injections up to a maximum of 24 injections in subsequent patients. An ultrasound examination was performed in all patients after completion of therapy. There were no procedure-related complications. Follow-up time in the first 11 patients was a minimum of 3 months. In these patients, all lesions <3 cm in diameter became negative on fine needle biopsy and showed volume reduction of up to 100 per cent on follow-up ultrasonography. However, lesions >3 cm in diameter remained positive for malignant cells and showed no evidence of regression sonographically. In the subsequent 17 patients, all lesions were sonographically smaller and negative on biopsy after a follow-up time ranging from 6 to 27 months. Eight of 12 lesions <2 cm in diameter were no longer detectable on ultrasound follow-up. Four lesions which were metachronously resected showed no viable tumour on histological assessment. Shina *et al.* achieved similar results in

14 patients with single hepatocellular lesions < 5 cm in diameter treated by alcohol injection alone[43]. The only complication reported was an intraperitoneal bleed in one patient 2 days after injection which settled on conservative management.

One problem is the difficulty in delineating the margins of a lesion after multiple alcohol injections. Sheu *et al.* addressed this by using a needle with multiple side holes and so injecting several sites in known juxtaposition. One or more small steel coils were implanted before treatment to serve as landmarks[44]. Six patients with solitary hepatocellular carcinomas < 3 cm in diameter were treated with this technique. Angiographic follow-up showed complete loss of the tumour blush in four and fine needle biopsy showed no viable tumour in five patients. Equivocally viable tumour was seen in one patient who underwent metachronous resection of a treated lesion. These results are impressive, but judging by the results of Livraghi *et al.*, small tumours (< 3 cm diameter) can do equally well after alcohol injection without steel coil insertion. The real issue is whether steel coil can improve results of alcohol injection when treating larger lesions.

Undoubtedly, percutaneous alcohol injection is an effective palliative and in some cases curative treatment for small hepatic tumours although the optimum volume and frequency of injection has not been determined. If one looks at all the data available on tumours ≤ 3 cm in diameter treated by alcohol injection in the Livraghi *et al.* and Sheu *et al.* series, and calculates the average volume of alcohol administered per lesion, then the variation in volume ranges from 5–10 ml per lesion[41] to 99 ml per lesion[44].

The volume of a tumour with a diameter of 3 cm, if assumed to be spherical, is only 17 ml. It is probable, therefore, that where large volumes of alcohol are injected, some alcohol diffuses to affect a rim of normal liver around the tumour which is desirable but it is also likely that areas already necrotic are being retreated. However, volumes of alcohol administered which are less than the volume of tumour probably leave residual viable areas of tumour. What is the ideal volume of alcohol which should be injected in relation to the volume of tumour under treatment? Based on a simple volume relationship and assuming homogeneous alcohol distribution throughout the tumour, the volume of alcohol injected should at least correspond to the volume of tumour being treated. However, it is known that when alcohol is injected, it will pass along planes of least resistance and therefore bypass areas of fibrous consistency which may be present from the outset or develop after the initial alcohol injection. Thus the distribution of alcohol is inhomogeneous and the biological effect becomes imprecise and unpredictable. This has been confirmed experimentally[45]. Therefore the ideal volume of alcohol injected and the optimum distribution of injection sites is based on guess-work. A second factor which contributes to the imprecision of alcohol therapy is that while alcohol may be seen sonographically diffusing through the tumour in real time, the all important biological effect becomes apparent from several minutes to several days after injection. Attempts to overcome the problems of localizing untreated areas of tumour after several alcohol injections by implantation of steel coils at the injection sites are as yet of unproven worth in large lesions. As an alternative, gelfoam has been used as it appears sonographically as a hyperechoeic shadow[46]. Unfortunately this appearance lasts for about 2 weeks only. Other problems include the passage of alcohol into nearby venous channels and the fact that large injection volumes are associated with severe pain. This pain is probably from retrograde flow of the alcohol along the needle tract with extravasation into the peritoneal cavity and may be controlled by limiting the volume of alcohol injected at any one site.

The case for alcohol injection is becoming stronger. Its advantages are many including minimal demand on manpower and equipment. The results for small lesions are promising. For example, Livraghi *et al.* reported a survival rate of 92 per cent after the first year in 12 patients treated with alcohol injections and this compares favourably with the results of resectional surgery for hepatocellular carcinoma of < 5 cm in diameter. In three surgical series of 28, 62 and 19 patients with such cancers, Shinagawa *et al.*, Lee *et al.* and Kinami *et al.* reported operative mortality rates of 10 per cent, 6 per cent and 12 per cent with 1-year survival rates of 78 per cent, 86 per cent and 80 per cent respectively[47–49]. The results of Livraghi *et al.* show that in selected patients, alcohol injection has the potential to cure and achieve results that are better than resectional surgery in terms of mortality and morbidity. Larger lesions may of course be treated with worthwhile regression but complete ablation with current techniques is unlikely.

Interstitial radiotherapy

Conventional external beam radiotherapy has little to recommend it for palliation of discrete hepatic metastases. There is a limit to the dose that can be applied to the liver because of the relative radiosensitivity of the hepatic parenchyma in comparison to a radioresistant tumour. A dose much above 3000 rads results in a significant incidence of radiation hepatitis, hepatic necrosis and biliary fibrosis[50]. In an attempt to overcome this problem, the technique of interstitial radiotherapy has been used. The rationale is that much higher doses can be delivered to the tumour with little effect on the normal surrounding parenchyma.

Nauta *et al.* treated 12 patients with inoperable metastatic disease of the liver at laparotomy by interstitial radiation using an iridium-192 source[51]. The lesions were located on the surface of the liver and the number of lesions treated varied from one to 11. The length of the procedure varied from 3 to 7·5 h. In ten patients with raised CEA levels before treatment, six showed a fall within 2·5 months of treatment. Computed tomographic evaluation at 1 week showed a halo of radio-oedema around the treated nodules. There were no procedure-related complications.

The invasive nature of 'open' interstitial radiation coupled with long operating times mitigates against the widespread use of this approach but Dritschilo *et al.* treated six patients with hepatic metastases from colorectal carcinoma using a high intensity iridium-192 source placed within the tumour percutaneously under ultrasound control[52]. The size of the lesions varied from 2·0 to 9·5 cm and a total of 11 procedures were performed. The first three patients in the series received a boost of external radiation. Follow-up at 1 month showed 25 per cent regression in one patient on ultrasonographic, and computed tomographic evaluation and the remainder showed non-progression of the treated lesion. All that can be said from these early results is that the technique is feasible; the follow-up is too short to comment on efficacy.

Interstitial radiotherapy has sound rationale for its use. However, at present there are considerable disadvantages with this technique when compared with other interstitial methods which have been discussed in this review. There seem to be few experimental data correlating interstitial radiation dosages with the nature and extent of the biological effect. This can be rectified but it is not possible to monitor the response to treatment in real time and interpretation of changes seen on follow-up computed tomographic imaging has not been fully studied. Further detailed work is necessary to determine the efficacy and safety of this approach before its true role can be identified.

Discussion

The prognosis for primary and metastatic liver cancer remains poor. In those patients who are unsuitable for surgery, current palliative treatments have little to offer in most cases and have an associated morbidity and mortality. Diffuse hepatic metastases is by far the commonest pattern of liver cancer seen in developed countries. Its management will remain a problem until a suitable infusional agent is developed. Interstitial techniques produce discrete areas of tissue necrosis and therefore have no role in such situations, although dominant lesions compressing vital structures may be debulked to alleviate symptoms. For the 5–10 per cent of patients with limited discrete hepatic metastases suitable for surgical resection, then at present this must remain the treatment of choice. If such patients are not amenable to hepatic resection on the grounds of inoperability or lack of fitness, then interstitial therapy may be offered as an alternative. It is these patients who are likely to derive most benefit from such an approach rather than left untreated. Similarly, small hepatocellular carcinomas in patients with severely compromised hepatic function or small functionally active endocrine tumours in symptomatic individuals may be treated with worthwhile palliation.

Interstitial methods have several advantages. They are effective at inducing necrosis of focal hepatic tumours by relatively non-invasive approaches. Morbidity and mortality rates are low, and hospitalization times are acceptably short except perhaps for patients treated by cryotherapy. The ability to damage neoplastic tissue selectively as compared with hepatic embolization where tissue destruction is non-selective is particularly valuable in those patients with hepatocellular carcinoma associated with cirrhosis; in such patients functioning hepatic tissue is at a premium. Retreatment in those patients who relapse is not constrained by cumulative tissue toxicity as with external radiotherapy and chemotherapy. Lesions which are inoperable because of close proximity to major vessels can be treated with relative safety by interstitial laser hyperthermia or cryotherapy as rapid blood flow within such vessels confers some protection to the vessel. It is possible that following interstitial treatment, inoperable lesions may become operable as tumour necrosis and resorption allow a surgical plane to become defined. However, the major biliary radicles are sensitive to thermal and cryogenic insult and inflammatory strictures may develop.

It is not clear which imaging technique is best for monitoring the effects of interstitial therapy at the time of treatment and during follow-up. Computed tomography, magnetic resonance imaging and angiography have all been used. Preliminary impressions suggest that ultrasonography can also fulfil such a role; it is non-invasive, easily repeated and relatively cheap. However, the resolution capability of ultrasound (lesion diameter $\geqslant 2$ cm) limits interstitial therapy to those tumours that can be reliably detected, although intraoperative use enhances considerably image resolution and quality. Once detected, the correlation between the limits of a lesion seen sonographically and its true extent is not clearly known. Therefore, for effective treatment, a 1 cm rim of 'normal' hepatic parenchyma beyond the obvious limit of a lesion should be incorporated into the treatment field. A policy of overtreatment would ensure maximum palliative benefit and increase the chances of cure in selected cases.

Which interstitial technique emerges as the best method available (*Table 1*)? Interstitial radiotherapy has not yet been fully evaluated and a question mark must remain over its role. Cryotherapy is effective but is also the most invasive of the interstitial methods. Patients not fit for a general anaesthetic or laparotomy are excluded and treatment of those who relapse is impractical. The technique is relatively demanding of nursing and medical manpower in part because of longer hospitalization times. The necessary equipment is relatively cheap compared with the price of a Nd:YAG laser but has fewer non-hepatic applications.

Alcohol injection has many factors in its favour, but there are limitations. At present, the therapeutic diameter limit is 3 cm for the size of lesion which may be eradicated, although larger lesions can be treated with effective control of tumour growth. However, the main problem is inhomogeneous distribution of alcohol within tumour tissue leading to unpredictable and imprecise areas of necrosis. Real time monitoring of the ensuing biological effect is not possible. Patients have to undergo several treatment sessions, be it on a day case basis.

Interstitial laser hyperthermia is the most effective of the thermal techniques. It is minimally invasive and produces predictable well-defined areas of necrosis. The size of lesion that can be treated satisfactorily is in the order of 2–3 cm in diameter with a 4-fibre system. On theoretical grounds, there is no limit to the number of fibres that can be inserted into the liver which is the limiting factor to the size of lesion that can be produced, although as yet there are no experimental data on the fate of areas of necrosis in the liver $>3{\cdot}5$ cm in diameter. Further research into dosimetry may reduce the number of treatment sessions currently necessary. As with all percutaneous techniques, not all parts of the liver are accessible to treatment. However, its precision and controllability compared with alcohol injection tips the balance in favour of interstitial laser hyperthermia. Further refinement in fibre design and increasingly sophisticated laser systems which monitor temperature and light distribution through the treated tissue indicate the way forward.

It may be argued that the impact of interstitial techniques will be limited as the number of patients suitable for treatment is small in relation to the total number of patients with liver cancer. However, it may be possible to identify further patients with increased use of hepatic intraoperative ultrasound monitoring at the time of resection of primary intra-abdominal

Table 1 *Relative merits of each of the interstitial techniques for liver cancer*

Criteria	Interstitial laser hyperthermia	Cryotherapy	Percutaneous alcohol injection	Percutaneous interstitial radiotherapy
Ease of application	+ + + +	+	+ + + + +	+ +
Precision and predictability	+ + + +	+ + + +	+ + +	+ + +
Ease of real time monitoring	+ + + +	+ + + +	+ +	Not possible
Accessibility to all liver	+ + + +	+ + + + +	+ + + +	+ + + +
Treatment frequency	+ + +	+ + + +	+ +	Unknown
Ease of retreatment	+ + + +	+	+ + + +	+ + +
Equipment expense	+	+ + +	+ + + + +	+ + +
Hospitalization time	+ + + +	+	+ + + + +	+ + + +
Staff required	Interventional radiologist	Surgeon, anaesthetist, theatre staff	Interventional radiologist	Interventional radiologist, physicist, radiotherapist

The greater the number of +, the greater the relative advantage (maximum five +)

cancers. Similarly, aggressive screening of patients at high risk of developing or harbouring asymptomatic focal hepatic lesions, e.g. cirrhotic patients, may yield further suitable patients.

The field of interstitial therapy is constantly moving. Undoubtedly advances in current treatment and follow-up techniques will occur allowing larger lesions to be treated with greater confidence and precision, less cost and easier follow-up. Current knowledge and development is such that treatment should now be considered for those patients with limited focal hepatic lesions which might otherwise have been left alone. Ultimately interstitial techniques may rival and improve upon the results of surgery with a lower morbidity and negligible mortality for suitably chosen patients.

References

1. Bengmark S. Palliative treatment of hepatic tumours. *Br J Surg* 1989; **76**: 771–3.
2. Fortner JG, Silva JS, Golbey BR *et al.* Multivariate analysis of a personal series of 247 consecutive patients with liver metastases from colorectal cancer. Treatment by hepatic resection. *Ann Surg* 1984; **199**: 306–16.
3. Okuda K. Primary liver cancers in Japan. *Cancer* 1980; **45**: 2663–8.
4. Lee NW, Wong J, Ong GB. The surgical management of primary carcinoma of the liver. *World J Surg* 1982; **6**: 66–75.
5. August DA, Sugarbaker PH, Ottow RT *et al.* Hepatic resection for colorectal metastases. *Ann Surg* 1985; **201**: 210–18.
6. Butler J, Attiyeh FF, Daly JM. Hepatic resection for metastases from the colon and rectum. *Surg Gynecol Obstet* 1986; **162**: 109–13.
7. Adson MA, van Heerden JA, Adson MH *et al.* Resection of hepatic metastases from colorectal cancer. *Arch Surg* 1984; **119**: 647–51.
8. Fortner JG. Recurrence of colorectal cancer after hepatic resection. *Am J Surg* 1982; **195**: 486–91.
9. Logan ES, Meier SJ, Ramming KP *et al.* Hepatic resection of metastatic colorectal carcinoma. *Arch Surg* 1982; **117**: 25–8.
10. Cady B, McDermott WW. Major hepatic resection for metachronous metastases from colon cancer. *Ann Surg* 1985; **201**: 204–9.
11. Taylor I. Colorectal metastases – to treat or not to treat. *Br J Surg* 1985; **72**: 511–16.
12. Breasted JH. *The Edwin Smith Surgical Papyrus.* Vol. 1. University of Chicago, 1930.
13. Milne JS. *Surgical Instruments in Greek and Roman Times.* Oxford: Clarendon Press, 1907.
14. Bleehen NM. Hyperthermia in the treatment of cancer. *Br J Cancer* 1982; **45**: 96–100.
15. King AJ, Williams DI, Nichol CS. Hyperthermia in the treatment of resistant gonococcal and non-specific urethritis. *Br J Ven Dis* 1943; **19**: 141–54.
16. Wallace J, Bushby SRM. Physiological and biochemical changes following hyperthermia treatment. *Br J Ven Dis* 1943; **19**: 155–66.
17. Cheung AY. Microwaves and radiofrequency techniques for clinical hyperthermia. *Br J Cancer* 1982; **45**: 16–24.
18. Hand JW, Ter-Haar G. Heating techniques in hyperthermia. *Br J Radiol* 1981; **54**: 443–66.
19. Hynynen K, Roemer R, Anhalts D *et al.* A scanned, focused, multiple transducer ultrasonic system for localized hyperthermia treatments. *Int J Hyperthermia* 1987; **3**: 21–35.
20. Bown SG. Phototherapy of tumours. *World J Surg* 1983; **7**: 700–9.
21. Matthewson K, Coleridge-Smith P, O'Sullivan JP *et al.* Biological effects of intrahepatic Nd:YAG photocoagulation in rats. *Gastroenterology* 1987; **93**: 550–7.
22. Steger AC, Bown SG, Clark CG. Interstitial laser hyperthermia: studies in the normal liver. *Br J Surg* 1988; **75**: A598.
23. Hashimoto D, Takami M, Ideezuki Y. In depth radiation therapy by Nd:YAG laser for malignant tumours of the liver under ultrasonic imaging. *Gastroenterology* 1985; **88**: A1663.
24. Schroder T, Hahl J. Laser induced hyperthermia in the treatment of liver tumours. *Lasers Surg Med* 1989; **Suppl 1**: A53.
25. Hetzel MR, Nixon C, Edmonston WM *et al.* Laser therapy in 100 tracheobronchial tumours. *Thorax* 1985; **40**: 341–5.
26. Beisland HO, Seland P. A prospective randomised study on neodymium YAG laser irradiation *versus* TUR in the treatment of urinary bladder cancer. *Scand J Urol Nephrol* 1986; **20**: 209–12.
27. Openchowaki PH. Sur l'action du froid applique a la surface de la region corticale du cerveau. *Compt Rend Soc Biol* 1883; **5**: 38–43.
28. Hass GM, Taylor CB. Quantitative hypothermal method for production of local injury of tissue. *Arch Pathol* 1948; **45**: 563–80.
29. Fay T. Refrigeration therapy. In: Glasser O, ed. *Medical Physics.* Chicago: Year Book Publishers, 1944: 1224–9.
30. Smith LW. Refrigeration in cancer: pathological observation in 100 advanced cases. *New York State J Med* 1940; **40**: 1355–61.
31. Lemariey A, Muler H. Essai d'application de la cryotherapie au traitment de la papillomatose laryngee infantile. *Ann Otolaryngol* 1960; **77**: 279–85.
32. Luyet BJ, Gehenio MP. *Life and Death at Low Temperatures.* Normandy, Missouri: Biodynamica, 1940: pp. 341.
33. Rowbotham JF, Haigh AL, Leslie WG. Cooling cannula for use in treatment of cerebral neoplasms. *Lancet* 1959; **i**: 12–15.
34. Zhou X-D, Tang Z-Y, Yu Y-Q, Ma Z-C. Clinical evaluation of cryosurgery in the treatment of primary liver cancer. *Cancer* 1988; **61**: 1889–92.
35. Ravikumar TS, Kane R, Cady B *et al.* Hepatic cryosurgery with intraoperative ultrasound monitoring for metastatic colon carcinoma. *Arch Surg* 1987; **122**: 403–9.
36. Jacob G, Li AKC, Hobbs KEF. A comparison of cryodestruction with excision or infarction of an implanted tumour in rat liver. *Cryobiology* 1984; **21**: 148–56.
37. Charnley RM, Doran J, Morris DL. Cryotherapy for liver metastases: a new approach. *Br J Surg* 1989; **10**: 1040–1.
38. Haaga JR, Kori Sh, Eastwod DW, Borkowski GP. Improved technique for CT guided coeliac ganglia block. *AJR* 1984; **142**: 1201–4.
39. Shinagawa T, Ukaji H, Lino Y *et al.* Intratumoral injection of absolute alcohol under ultrasound imaging for the treatment of small hepatocellular carcinoma: attempts in 3 cases. *Acta Hepatol Jpn* 1985; **26**: 99–105.
40. Fujimoto T, Majima Y, Tanaka M *et al.* Investigation of percutaneous ultrasonographically guided ethanol injection therapy. *Acta Hepatol Jpn* 1986; **27**: 1559–67.
41. Livraghi T, Festi D, Monti F *et al.* US-guided percutaneous alcohol injection of small hepatic and abdominal tumours. *Radiology* 1986; **61**: 309–12.
42. Livraghi T, Salmi A, Bolondi L *et al.* Small hepatocellular carcinoma: percutaneous alcohol – results in 23 patients. *Radiology* 1988; **168**: 313–17.
43. Shina S, Yasuda H, Muto H *et al.* Percutaneous ethanol injection in the treatment of liver neoplasms. *AJR* 1987; **149**: 949–52.
44. Sheu J-C, Huang G-T, Chen D-S *et al.* Small hepatocellular carcinoma: intratumoral ethanol treatment using a new needle and guidance system. *Radiology* 1987; **163**: 43–8.
45. Rutgeerts P, Hiele M, Vantrappen G *et al.* Treatment of hepatic tumours with laser hyperthermia: a comparison with alcoholisation. *Lasers Med Sci* 1990; Abstract edition p. 30.
46. Shina S, Komatsu Y, Shiratori Y *et al.* Sonographically guided percutaneous injection of ethanol for treatment of hepatocellular carcinoma: value of gelfoam to mark the lesion. *AJR* 1989; **153**: 430.
47. Shinagawa T, Ohto M, Kimura K *et al.* Diagnosis and clinical features of small hepatocellular carcinomas with emphasis on the utility of real time ultrasonography: a study in 51 patients. Gastroenterology 1984; **86**: 495–502.
48. Lee CS, Sung JL, Hwang LY *et al.* Surgical treatment of 109 patients with symptomatic and asymptomatic hepatocellular carcinoma. *Surgery* 1986; **99**: 481–90.
49. Kinami Y, Takashima S, Miyazaki I. Hepatic resection for hepatocellular carcinoma associated with liver cirrhosis. *World J Surg* 1984; **199**: 51–6.
50. Gunderson LL, Tepper JE, Biggs PJ *et al.* Intraoperative plus or minus external beam irradiation. *Curr Probl Cancer* 1983; **7**: 1–93.
51. Nauta RJ, Heres EK, Thomas DS *et al.* Intraoperative single dose radiotherapy. *Arch Surg* 1987; **122**: 1392–5.
52. Dritschilo A, Grant EG, Harter KW *et al.* Interstitial radiation therapy for hepatic metastases: sonographic guidance for applicator placement. *AJR* 1986; **146**: 275–8.

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Review

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Adult polycystic disease of the liver

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Adult polycystic liver disease (APLD) is a rare disorder of liver parenchyma occasionally requiring surgical treatment. Its association with adult polycystic kidney disease has meant that as renal dialysis has become widely available there is an increased number of patients surviving with cystic liver changes. Although usually asymptomatic, patients with APLD may present with abdominal pain or swelling. Liver function is not usually compromised and computed tomography or abdominal ultrasonography are the most useful investigations. The complications of cyst rupture, infection, cholangiocarcinoma and compression of surrounding structures are discussed. Surgical treatment remains controversial, and the options of cyst puncture, fenestration with or without hepatic resection, and liver transplantation are reviewed.

Adult polycystic liver disease (APLD), first described in 1856 by Bristowe in association with polycystic kidney disease[1], is a rare disorder of the liver parenchyma occasionally requiring surgical treatment. It is characterized by multiple diffuse cystic lesions within the liver which may cause symptoms or which may come to light as incidental findings. This review examines the current state of knowledge regarding the pathogenesis of the disease. The treatment of symptomatic disease is still controversial and usually requires surgical intervention.

Genetic basis and pathology

Until recently APLD and adult polycystic kidney disease (APKD) were thought to represent a single dominantly inherited genetic entity. The gene responsible for APKD has been located on human chromosome 16 and predictive DNA analyses have been developed for presymptomatic and prenatal diagnosis[2].

The existence of APLD as a separate entity was raised by Norio[3] and Berrebi *et al.*[4]. Karhunen and Tenhu[5] in 1986 suggested that it is indeed a separate entity. However, if this is so, the exact mode of its genetic transmission is yet to be established.

APLD is characterized by a gradual cystic transformation of both lobes of the liver. The exact incidence and association between polycystic kidney and liver disease has recently been studied using systematic computed tomography (CT) scan analysis of patients with APKD. The variable association of APLD and APKD reported relates to the age and sex distribution of the populations studied and the duration of the observation. The number of cysts found correlates with the age of the patients[6,7]. While up to 93 per cent of patients with APLD have associated APKD[7,8], systematic studies show that 34–78 per cent of patients with APKD have cystic livers[7,9–12]. Although APLD is most commonly associated with APKD, families with APLD without kidney disease have now been described[3,4,13].

In 1–3 per cent of patients cysts are present in organs and tissues other than liver and kidney (pancreas, spleen, omentum, lungs and ovaries)[14,15]. Although usually recognized only in adult life, APLD has been observed at all ages[16–18].

Cyst distribution and structure

The cysts of APLD vary in size from small, microscopic cysts to large cysts containing several litres of fluid[19,20]. The liver is enlarged, sometimes extending from the diaphragm to the pubis[21]. Volumetric measurement of parenchyma using CT scanning indicates that hepatic parenchymal volume is preserved in APLD despite massive cyst formation[22].

The wall of the liver cysts consists of three layers as described by Gaviser[23]; an inner loose connective tissue layer lined with cylindrical or cuboidal epithelium, a middle layer of compact connective tissue containing blood vessels, and an outer layer of loose connective tissue with large blood vessels and bile ducts and occasional von Meyenburg complexes. The epithelial lining may disappear as a result of high intracystic pressure[24]. This arrangement explains the inability to enucleate hepatic cysts without causing major bleeding[25]. In APLD most cysts contain clear (i.e. serous) fluid but brown (i.e. haemorrhagic) or bile-stained cysts are also described. The fluid within clear cysts has almost no albumin or protein and the electrolyte concentration is similar to that of serum[26–28]. Such fluid is not irritating to peritoneal surfaces[29]. Following haemorrhage into a cyst the fluid becomes brown and dark, protein and albumin contents rise, and the fluid tests positive for haemoglobin. Bile-stained cysts are rare in polycystic livers[30,31] but deserve particular attention because bile radicals are often noted in their walls[32,33]

Pathogenesis of cysts

Distinction between APLD and simple cysts of the liver can sometimes be difficult at an early stage because the cysts of patients with APLD are histologically no different from simple cysts, which can also be multiple. However, in contrast to APLD, simple hepatic cysts do not eventually result in diffuse involvement of the parenchyma, have no familial incidence, and are not accompanied by cystic involvement of other organs[15,34].

Moschcowitz attributed cyst formation to obstruction of aberrant bile ducts[35]. Von Meyenburg theorized that the intralobular bile ducts (proximal anlage) which fail to involute or connect with the extralobular bile ducts (distal anlage) result in cyst formation with fluid accumulation[36]. Melnick in 1955 saw a confirmation of this hypothesis in the presence of many islands of ductular epithelium in cyst walls[14]. These islets of bile ducts outside the portal spaces are now described as von Meyenburg complexes.

The autopsy prevalence of APLD was reported to be 0·03 per cent in 1959[37] but in 1988 was found to be 0·13 per cent[8]. This difference is probably due to the increasing number of patients surviving kidney involvement as a result of dialysis, thus allowing the development of the liver disease. The reported male:female ratio is between 1:2 and 1:4 in most series[15,19,38]. Kaehny *et al.* found an increased prevalence of cysts in women, the number of cysts correlating directly with the number of pregnancies[38]. This would suggest that the development of APLD is influenced, as is normal liver, by the oestrogenic environment.

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Presentation

The disease usually remains asymptomatic for a long time. A large liver in the absence of any symptoms is in fact the hallmark of the disease. However, many patients do develop symptoms over time. In Peltokallio's extensive study from Finland[15], APLD caused severe symptoms or complications in 20 of 102 patients. However, as many as 54 of 105 patients with less dominant symptoms spontaneously consulted their physician.

The disease usually manifests itself between 40 and 60 years of age. The patient complains of abdominal swelling (23 per cent), intermittent attacks of pain (22 per cent), pain on stooping (17 per cent), or dyspnoea (10 per cent). It is difficult to correlate the symptoms with the size of the liver. Peltokallio reports six patients able to work normally with a liver close to the pubic symphysis while three patients were completely incapacitated with livers from six to ten finger-breadths below the costal margin. Haemorrhage into a cyst is thought to be responsible for the acute attacks of pain described in APLD[39].

Investigation

While renal function is often impaired in APLD, liver function tests are almost always normal with only 10–20 per cent of patients having abnormal values, notably increased serum alkaline phosphatase levels[15]. Therefore when the results of liver function tests are abnormal one should first rule out associated disease[40]. Impairment of drug metabolism is demonstrable in patients with APLD, who have a prolonged plasma antipyrine half-life and a decreased high density lipoprotein cholesterol synthesis when compared with other family members without the disease[13,41]. These studies suggest that although the parenchymal liver mass is unchanged there is a relative impairment of active liver parenchyma.

Recent advances in imaging techniques have outdated many previous examinations. Liver scintigraphy is now obsolete because it cannot differentiate between solid and cystic lesions or demonstrate cysts smaller than 20 mm in diameter[12]. While plain abdominal radiographs can occasionally show extensive calcification[42] or a mass effect suggesting liver enlargement, both ultrasonography and CT scanning are accurate in delineating the anatomy of the cystic transformation.

Recently, magnetic resonance imaging has allowed definition of the density of cyst content and could in future help to localize intracystic haemorrhage and infection[43].

Complications

Acute complications are more frequently associated with renal cysts than hepatic cysts[19]. Indeed the prognosis of APLD is determined by the prognosis of the kidney disease[43]. In addition, hypertension as a consequence of kidney disease and the association of cerebral aneurysms (10–20 per cent)[8] result in a high incidence of cerebrovascular accidents in patients with APLD[9,44].

The overall incidence of acute hepatic complications such as jaundice, infection or haemorrhage is low in APLD and did not exceed 5 per cent overall in Peltokallio's series[15]. More recent reports suggest that liver complications account for over 10 per cent of deaths in patients with APLD, patients who are now surviving their renal disease as a result of dialysis[45].

Jaundice has been variably reported in APLD. Large series often mention patients with a mild increase in serum bilirubin or alkaline phosphatase levels[15,19,28]. Frank jaundice can occur secondary to cyst compression[28,46–48], a common bile duct stone[49,50] or possibly a bile duct tumour. Preoperative endoscopic retrograde cholangiography will demonstrate extrinsic cystic compression or exclude a bile duct tumour. Small intrahepatic cysts sometimes mimick intraductal stones and only direct vizualization at choledochoscopy will exclude gallstone disease[50].

When septic complications of hepatic cysts do occur they are devastating and often lead to liver failure and death[51–55]. *Escherschia coli* septicaemia originating from an infected hepatic cyst is often present[56,57]. This can be confusing in patients with end-stage APKD because bacterial sepsis is also a frequent complication of haemodialysis[58,59]. In the absence of local clinical findings, a ^{111}In-labelled leucocyte scan can be useful in localizing the source of sepsis[57].

In spite of the large epithelial surface developed by the cysts and von Meyenburg complexes, the occurrence of carcinoma in APLD is rare. A few cases of carcinomas arising in simple cysts have been described[60–64], but only four cases of cholangiocarcinoma arising in patients with APLD have been reported[45,65]. In these cases the prognosis is very poor, death occurring within 6 months of diagnosis. This low incidence of carcinoma is probably related to the non-communicating nature of the cysts and the absence of the irritant effects of bile stasis[66].

Extrahepatic complications

Because renal cysts communicate directly with the urinary tract, renal cyst infections occur more frequently than hepatic cyst infections in patients with APLD[56,67]. While portal hypertension causes significant morbidity and mortality rates in childhood fibrocystic liver disease (congenital hepatic fibrosis)[68], bleeding from oesophageal varices is very rare in APLD. There is no fibrosis and the portal spaces are preserved. Up to now, only five adults with polycystic livers have been reported to have bled from oesophageal varices[69–72]. Although some authors[18,58] have doubted that APLD could cause portal hypertension, a recent report of the disapperance of oesophageal varices following a fenestration procedure confirms that APLD can be associated with portal hypertension, presumably as a result of portal vein compression[28].

Treatment

Prophylactic

When treating patients with APLD, attention should be directed not only towards the patient but also the family. In particular the associated anxiety of other family members who may also be affected by APLD, as well as concern for the individual patient's prognosis, should be discussed. Screening of the children and other family members for unrecognized hypertension and ultrasonography of the kidney and liver are simple non-invasive precautions. The risk of an associated cerebral aneurysm should be explained and, if necessary, investigation should be considered.

Efficient prevention of APLD associated with APKD can now be achieved by genetic counselling and early prenatal diagnosis based on DNA analyses of chorionic villi cells[73].

Aspiration and sclerosis

While simple aspiration is followed by recurrence in almost all cases[28,74], hepatic cyst sclerosis with alcohol or other agents is appropriate for simple cysts[75,76] and for the occasional patient with APLD whose symptoms can be clearly attributed to compression symptoms from a single large cyst[77,78]. The early experience with this treatment suggests that the sclerosing effect of alcohol on the cyst wall prevents recurrence or infection, both of which commonly occur after fine needle aspiration alone. Although this technique seems to have offered good results in some hands[77], failure has been reported and long-term results are not available[79]. The risk of infection, together with the high failure rate, has discouraged the present authors from using this technique. In addition it is contraindicated in cysts containing bile.

Transhepatic fenestration

For the diffusely scattered or deeply seated lesions of most patients with APLD, only a surgical approach will provide permanent relief. In 1968 Lin *et al.* described a transhepatic

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fenestration procedure in three patients with disabling polycystic livers[26], in which they stated 'resection was impossible, so all large cysts were widely opened and tunnelled into each other and to the free peritoneal cavity'. No tamponade or other measures to obliterate the cyst cavities or external drainage were used. Isolated cases of Lin *et al.*'s fenestration operation have been reported[15,32,80–83] but the subsequent follow-up is short. One case of recurrence after fenestration has been described and necessitated reoperation[32].

Van Erpecum *et al.*[28] described nine patients (seven with abdominal pain and two with obstructive jaundice) treated by transhepatic fenestration. Eight patients had relief of their symptoms including disappearance of jaundice and one patient died perioperatively. The authors admitted that the liver size was not reduced by fenestration and attributed the relief of pain to reduction in cyst tension. The mean length of follow-up of these patients was 4 years but their subsequent work capacity was not mentioned.

Fenestration and resection

For this reason many authors have performed liver resection with or without transhepatic fenestration for APLD[29,31,49,79,83] with good results. Turnage *et al.*[82] reported a poor outcome in two of three patients who had undergone fenestration and resection but one was a reoperation and the other died from cardiac tamponade secondary to the insertion of a central line. The major advantage of fenestration and resection is the return to a normal body habitus and stimulation of regeneration of liver parenchyma[31].

When fenestration and/or resection are used to treat APLD, the postoperative course is often prolonged with significant morbidity[27,31], and there is still room for improvement. The main problem relates to massive perioperative fluid losses[31,81] which can lead to severe dehydration. Lin *et al.*[26] did not drain their patients after fenestration and reported no complication, while Huguet *et al.*[27] resorted to repeated peritoneal tapping to relieve large amounts of ascites. The amount of fluid draining can readily exceed the capacity of resorption of the peritoneum[84]. Secretin directly influences biliary secretion[85,86] and probably affects the epithelial lining of the cysts. Cimetidine, which indirectly diminishes secretin output, has been used successfully to decrease the amount of postoperative drainage[32]. Somatostatin, which has a direct action on secretin, may also reduce drainage[87].

In six patients requiring operation for symptomatic APLD we have elected to use the technique of fenestration and resection, and this approach was also used recently by others in eight highly symptomatic patients with APLD[44]. In addition, we have now adopted a policy of immediate postoperative use of long-acting somatostatin (octzeotide) and H_2-receptor blocker treatment with good effect. We have recently had successful experience in four patients without drainage following fenestration and resection, and believe that this approach can improve the postoperative course of patients with APLD.

Hepatic and renal transplantation

The optimum treatment for patients with symptomatic APLD and renal failure is not clear. Hepatic surgery in the presence of renal failure is more hazardous. Combined single donor hepatic and renal transplantation offers an alternative solution, but experience in this situation is limited[8,44,88].

Conclusion

APLD continues to pose a number of challenges. Close screening of the family for undiagnosed APLD and its complications is necessary. A better understanding of its genetic base and development may lead to prophylactic treatment options. Pharmacological agents with proven ability to suppress cyst production are required. The timing of operation and optimal surgical approach still need to be clearly defined. However, at present in patients who are highly symptomatic we recommend hepatic fenestration and resection (without drainage) combined with suppression of cyst secretion.

References

1. Bristowe, F. Cystic disease of the liver associated with a similar disease of the kidneys. *Trans Pathol Soc Lond* 1856; **7**: 229–34.
2. Reeders ST, Breuning MH, Davies KE *et al.* Adult polycystic kidney disease is linked to the alpha-globulin and phosphoglycolate phosphatase loci on chromosome 16. *Cytogenet Cell Genet* 1985; **40**: 729.
3. Norio R. Polycystic disease of liver: an entity of its own or not? *Clin Genet* 1983; **23**: 78–80.
4. Berrebi G, Erickson RP, Marks BW. Autosomal dominant polycystic liver disease: a second family. *Clin Genet* 1982; **21**: 342–7.
5. Karhunen PJ, Tenhu M. Adult polycystic liver and kidney diseases are separate entities. *Clin Genet* 1986; **30**: 29–37.
6. Milutinovic J, Fialkow PJ, Rudd TG, Agodoa LY, Phillips LA, Bryant JI. Liver cysts in patients with autosomal dominant polycystic kidney disease. *Am J Med* 1980; **68**: 741–4.
7. Feldman M. Polycystic disease of the liver. *Am J Gastroenterol* 1958; **29**: 83–6.
8. Kwok MK, Lewin KJ. Massive hepatomegaly in adult polycystic liver disease. *Am J Surg Pathol* 1988; **12**: 321–4.
9. Iglesias CG, Torres VE, Offord KP, Holley KE, Beard CM, Kurland LT. Epidemiology of adult polycystic kidney disease, Olmsted County, Minnesota: 1935–1980. *Am J Kidney Dis* 1983; **2**: 630–9.
10. Nagorney DM, Torres VE, Rakela J, Welch TJ. Surgical anatomy of the liver in adult polycystic kidney disease (APKD). *Kidney Int* 1988; **33**: 202.
11. Levine E, Cook LT, Grantham JJ. Liver cysts in autosomal-dominant polycystic kidney disease: clinical and computed tomographic study. *AJR* 1985; **145**: 229–33.
12. Thomsen HS, Thaysen JH. Frequency of hepatic cysts in adult polycystic kidney disease. *Acta Med Scand* 1988; **224**: 381–4.
13. Sotaniemi EA, Luoma PV, Järvensivu PM, Sotaniemi KA. Impairment of drug metabolism in polycystic non-parasitic liver disease. *Br J Clin Pharmacol* 1979; **8**: 331–5.
14. Melnick PJ. Polycystic liver. *Arch Pathol* 1955; **59**: 162–72.
15. Peltokallio V. Non-parasitic cysts of the liver. A clinical study of 117 cases. *Ann Chir Gynaecol* 1970; **59**(Suppl 174): 1–63.
16. Blyth H, Ockenden BG. Polycystic disease of kidneys and liver presenting in childhood. *J Med Genet* 1971; **8**: 257–84.
17. Rosenfield AT, Lipson MH, Wolf B, Taylor KJW, Rosenfield NS, Hendler E. Ultrasonography and nephrotomography in the presymptomatic diagnosis of dominantly inherited (adult-onset) polycystic kidney disease. *Radiology* 1980; **135**: 423–7.
18. Milutinovic J, Schabel SI, Ainsworth SK. Autosomal dominant polycystic kidney disease with liver and pancreatic involvement in early childhood. *Am J Kidney Dis* 1989; **13**: 340–4.
19. Comfort MW, Gray HK, Dahlin DC, Whitesell FB. Polycystic disease of the liver: a study of 24 cases. *Gastroenterology* 1952; **20**: 60–78.
20. Burch JC, Jones HE. Large nonparasitic cyst of the liver simulating an ovarian cyst. *Am J Obstet Gynecol* 1952; **63**: 441–4.
21. Chaffin L. Congenital cystic disease of the liver. *West J Surg Obstet Gynecol* 1948; **56**: 193–9.
22. Everson GT, Scherzinger A, Berger-Leff N *et al.* Polycystic liver disease: quantitation of parenchymal and cyst volumes from computed tomography images and clinical correlates of hepatic cysts. *Hepatology* 1988; **8**: 1627–34.
23. Gaviser D. Solitary nonparasitic cysts of the liver. *Minn Med* 1953; **36**: 831–49.
24. Daroczi G, Metzl J. Polyzystische Leber. *Beitr Klin Chir* 1958; **197**: 337–42.
25. Moreaux J, Bloch P. Les kystes biliaries solitaires du foie. *Arch Fr Mal App Dig* 1971; **60**: 203–24.
26. Lin TY, Chen CC, Wang SM. Treatment of non-parasitic cystic disease of the liver: a new approach to therapy with polycystic liver. *Ann Surg* 1968; **168**: 921–7.
27. Huguet C, Hecht Y, Ricordeau P, Caroli J. Les énormes polykystoses hépatiques. *Med Chir Dig* 1973; **2**: 227–30.
28. Van Erpecum KJ, Janssens AR, Terpstra JL, Tjon A Tham RTO.

Highly symptomatic adult polycystic disease of the liver. *J Hepatol* 1987; **5**: 109–17.

29. Lanson SZ, Frieden JH, Bierman HR. Polycystic disease of the liver. *JAMA* 1971; **215**: 793–4.
30. Longmire WP, Mandiola SA, Gordon HE. Congenital cystic disease of the liver and biliary system. *Ann Surg* 1971; **174**: 711–24.
31. Armitage NC, Blumgart LH. Partial resection and fenestration in the treatment of polycystic liver disease. *Br J Surg* 1984; **71**: 242–4.
32. Paliard P, Partensky C. Traitement par fenestration itérative d'une forme douloureuse, puis cholestatique de polykystose hépatique. *Gastroenterol Clin Biol* 1980; **4**: 854–7.
33. Litwin DEM, Taylor BR, Greig P, Langer B. Nonparasitic cysts of the liver: the case for conservative surgical management. *Ann Surg* 1987; **205**: 45–8.
34. Uggerud R. Solitaere, ikke-parasitaere levercyster. *T Norsk Laegeforen* 1965; **85**: 831–3.
35. Moschcowitz E. Non-parasitic cysts (congenital) of the liver with a study of aberrant bile ducts. *Am J Med Sci* 1906; **131**: 674–99.
36. Von Meyenburg H. Ueber die Cystenleber. *Beitr Pathol Anat* 1918; **64**: 477–531.
37. South C, Haugh WA. Congenital polycystic disease of the liver. *Arch Pathol* 1959; **67**: 650–5.
38. Kaehny WD, Manco-Johnson M, Johnson AM, Tangel DJ, Gabow PA. Influence of sex on liver manifestation of autosomal dominant polycystic kidney disease (ADPK). *Kidney Int* 1988; **33**: 196.
39. Ackman FD, Rhea LJ. Non-parasitic cysts of the liver: their clinical and pathological aspects. *Br J Surg* 1931; **18**: 648–54.
40. Cryer PE, Kissane JM. Obstructive jaundice in a patient with polycystic disease. *Am J Med* 1977; **62**: 616–26.
41. Luoma PV, Sotaniemi EA, Ehnholm C. Low high-density lipoprotein and reduced antipyrine metabolism in members of a family with polycystic liver disease. *Scand J Gastroenterol* 1980; **15**: 869–73.
42. Kutcher R, Schneider M, Gordon DH. Calcification in polycystic disease. *Radiology* 1977; **122**: 77–80.
43. Davis PL, Kanal E, Farnum GN, van Thiel DH, Iwatsuki SM. MR imaging of multiple hepatic cysts in a patient with polycystic liver disease. *Magn Reson Imaging* 1987; **5**: 407–11.
44. Newman KD, Torres VE, Rakala J, Nagorney DN. Treatment of highly symptomatic polycystic liver disease. *Ann Surg* 1990; **212**: 30–7.
45. Grünfeld JP, Albouze G, Jungers P *et al.* Liver changes and complications in adult polycystic kidney disease. *Adv Nephrol* 1985; **14**: 1–20.
46. Wittig JH, Burns R, Longmire WP. Jaundice associated with polycystic liver disease. *Am J Surg* 1978; **136**: 383–6.
47. Howard RJ, Hanson RF, Delaney JP. Jaundice associated with polycystic liver disease. *Arch Surg* 1976; **111**: 816–17.
48. Ergün H, Wolf BH, Hissong SL. Obstructive jaundice caused by polycystic liver disease. *Radiology* 1980; **136**: 435–6.
49. Jones WL, Mountain JC, Warren KW. Symptomatic non-parasitic cysts of the liver. *Br J Surg* 1974; **61**: 118–23.
50. Heather B. Choledochoscopic appearance of hepatic ducts in polycystic disease of the liver. *J R Soc Med* 1978; **71**: 526–9.
51. Davis CR. Non-parasitic cysts of liver. *Am J Surg* 1937; **35**: 590–4.
52. Robson GB, Fenster LF. Fatal liver abscess developing in a polycystic liver. *Gastroenterology* 1964; **47**: 82–4.
53. Bennett AH, Stewart W, Lazarus JM. Bilateral nephrectomy in patients with polycystic renal disease. *Surg Gynecol Obstet* 1973; **137**: 819–20.
54. Wrong O. A case of polycystic disease of the liver and kidneys. *Br Med J* 1965; **2**: 1356–8.
55. Deutsch E. Congenital cystic disease of the kidneys and liver complicated by cholangitis; case report. *Gastroenterology* 1953; **23**: 92–6.
56. Bourgeois N, Kinnaert P, Vereerstraeten P, Schoutens A, Toussaint C. Infection of hepatic cysts following kidney transplantation of polycystic disease. *World J Surg* 1983; **7**: 629–31.
57. Gesundheit N, Kent DL, Fawcett HD, Effron MK, Maffly RH. Infected liver cyst in a patient with polycystic kidney disease. *West J Med* 1982; **136**: 246–9.
58. Dobkin JF, Miller MH, Steigbigel NH. Septicemia in patients on chronic hemodialysis. *Ann Intern Med* 1978; **88**: 28–33.
59. Nsouli KA, Lazarus JM, Schoenbaum SC, Gottlieb MN, Lowrie EG, Shocair M. Bacteremic infection in hemodialysis. *Arch Intern Med* 1979; **139**: 1255–8.
60. Willis RA. Carcinoma arising in congenital cysts of the liver. *J Pathol* 1943; **55**: 492–5.
61. Richmond HG. Carcinoma arising in congenital cysts of the liver. *J Pathol Bacteriol* 1956; **72**: 681–3.
62. Greenwood N, Orr WMcN. Primary squamous-cell carcinoma arising in a solitary non-parasitic cyst of the liver. *J Pathol* 1972; **107**: 145–8.
63. Ameriks J, Appleman H, Frey C. Malignant nonparasitic cyst of the liver. *Ann Surg* 1972; **176**: 713–17.
64. Imamura M, Miyashita T, Tani T, Naito A, Tobe T, Takahashi K. Cholangiocellular carcinoma associated with multiple liver cysts. *Am J Gastroenterol* 1984; **79**: 790–5.
65. Azizah N, Paradinas FJ. Cholangiocarcinoma coexisting with developmental liver cysts: a distinct entity different from liver cystadenocarcinoma. *Histopathology* 1980; **4**: 391–400.
66. Bloustein PA. Association of carcinoma with congenital cystic conditions of the liver and bile ducts. *Am J Gastroenterol* 1977; **67**: 40–6.
67. Abascal J, Moya M, Martin F. Infection of hepatic cysts in polycystic disease. *World J Surg* 1984; **8**: 424–5.
68. Benhamou JP, Menu Y. Non parasitic cystic diseases of the liver and intrahepatic biliary tree. In: Blumgart LH, ed. *Surgery of the Liver and Biliary Tract.* Edinburgh: Churchill Livingstone, 1988: 1018–20.
69. Katzen NG. Fatal hepatic polycystic disease. *Br Med J* 1964; **1**: 839–40.
70. Campbell GS, Bick HD, Paulson EP, Lober PH, Watson CJ, Varco RL. Bleeding esophageal varices with polycystic liver. *N Engl J Med* 1958; **259**: 904–10.
71. Del Guercio E, Greco J, Kim KE, Chinitz J, Swartz C. Esophageal varices in adult patients with polycystic kidney and liver disease. *N Engl J Med* 1973; **289**: 678–9.
72. Ratcliffe PJ, Reeders S, Theaker JM. Bleeding oesophageal varices and hepatic dysfunction in adult polycystic kidney disease. *Br Med J* 1984; **288**: 1330–1.
73. Dalgaard OZ, Nrby S. Autosomal dominant polycystic kidney disease in the 1980s. *Clin Genet* 1989; **36**: 320–5.
74. Saini S, Mueller PR, Ferrucci JT, Simeone JF, Wittenberg J, Butch RJ. Percutaneous aspiration of hepatic cysts does not provide definitive therapy. *AJR* 1983; **141**: 559–60.
75. Bean WJ, Rodan BA. Hepatic cysts: treatment with alcohol. *AJR* 1985; **144**: 237–41.
76. Goldstein HM, Carlyle DR, Nelson RS. Treatment of symptomatic hepatic cyst by percutaneous instillation of Pantopaque. *Am J Roetgenol* 1976; **127**: 850–3.
77. Kairaluoma MI, Leinonen A, Stahlberg M, Päivänsalo M, Kiviniemi H, Siniluoto T. Percutaneous aspiration and alcohol sclerotherapy for symptomatic hepatic cysts. *Ann Surg* 1989; **210**: 208–15.
78. Trinkl W, Sassaris M, Hunter FM. Nonsurgical treatment for symptomatic nonparasitic liver cyst. *Am J Gastroenterol* 1985; **80**: 907–11.
79. Iwatsuki S, Starzl TE. Personal experience with 411 hepatic resections. *Ann Surg* 1988; **208**: 421–32.
80. Maillet P, Brette R, Bertrand JL, Tissot E. Trois cas de polykystose hepato-renale. *Lyon Med* 1973; **230**: 439–42.
81. Favre JP, Cayot M, Faivre J, Trigalou D, Klepping C, Viard H. La maladie polykystique du foie. *Rev Fr Gastroenterol* 1978; **142**: 25–30.
82. Turnage RH, Eckhauser FE, Knol JA, Thompson NW. Therapeutic dilemmas in patients with symptomatic polycystic liver disease. *Am Surg* 1988; **54**: 365–72.
83. Henson SW, Gray HK, Dockerty MB. Benign tumors of the liver. IV. Polycystic disease of surgical significance. *Surg Gynecol Obstet* 1957; **104**: 63–7.
84. Shear L, Ching S, Gabuzda GJ. Compartmentalization of ascites and edema in patients with hepatic cirrhosis. *N Engl J Med* 1970; **282**: 1391–6.
85. Erlinger S, Dhumeaux D. Mechanisms and control of secretion of bile water and electrolytes. *Gastroenterology* 1974; **66**: 281–304.
86. Turnberg LA, Jones EA, Sherlock S. Biliary secretion in a patient with cystic dilatation of the intrahepatic biliary tree. *Gastroenterology* 1968; **54**: 1155–61.
87. Boden G, Sivitz MC, Owen OE. Somatostatin suppresses secretin and pancreatic exocrine secretion. *Science* 1975; **190**: 163–5.
88. Starzl TE, Reyes J, Tzakis A, Micles L, Todos Gordon R. Liver transplantation for polycystic liver disease. *Arch Surg* 1990; **125**: 575–7.

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Steroid receptors in breast cancer

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Recent advances in steroid receptor structure and function now indicate that oestrogen binds to the oestrogen receptor (ER) molecule at a specific site, denoted region E. This allows binding of the oestrogen–ER complex to DNA via cysteine residues in region C of the ER molecule, which tetrahedrally co-ordinate zinc. This modulates transcription and stimulates cell growth. A number of newly discovered growth factors are also regulated by ER, as is the progesterone receptor. Steroid receptor concentrations in tissues can now be measured on smaller tissue samples using enzyme immunoassay or on cells obtained by fine needle aspiration using monoclonal antibody technology. The prognostic value of steroid receptor is limited, but still constitutes the best marker for predicting response to endocrine therapy. The role of steroid receptors in selecting patients for adjuvant therapy is discussed.

There is now a substantial body of epidemiological evidence implicating oestrogens in the development of breast cancer[1]. It has been known for almost a century that hormonal manipulation in advanced breast cancer causes regression of the disease in approximately 30 per cent of patients[2,3]. *In vitro*, human breast cancer cell lines derived from patients' pleural or ascitic fluid have been used to demonstrate a direct proliferative response to physiological doses of oestrogen[4]. The discovery of oestrogen receptors[5] gave fresh impetus to investigating the inter-relationships between oestrogen and mammary cell growth and carcinogenesis. As a result, a variety of growth factors[6–21] and oestrogen-inducible proteins[22–28] have now been discovered, and a variety of enzyme changes have been noted when oestrogens act on breast cells *in vitro*[6]. Most of these proteins are regulated via the oestrogen receptor (ER) mechanism. These studies are beginning to give some insight into the pathophysiology of oestrogen action in mammary carcinogenesis and an excellent review of the subject has been published recently[7]. However, despite intensive studies, the molecular mechanisms by which oestrogen regulates the growth of breast cancer cells are still poorly understood. With the help of molecular biology, some of these mechanisms are now beginning to be elucidated.

A deeper understanding of these mechanisms might help to identify more precisely how endocrine treatments exert their cytostatic effects. It may also reveal why the current markers of hormone responsiveness of tumours (namely oestrogen and progesterone receptor concentrations) are imperfect. Better markers of endocrine response may be discovered and new therapeutic strategies devised.

This article reviews recent advances in steroid receptor measurement used in clinical practice and the scientific advances in our knowledge of receptor structure and function. The clinical relevance of steroid receptors is discussed, as well as the reasons for some of the contradictory results of clinical studies.

Structure and function of oestrogen receptors

Oestrogens were once thought to exert their action on target cells by diffusing through the cell membrane and binding to their specific receptors in the cytoplasm. After binding, the oestrogen–receptor complex translocated to the cell nucleus[29]. However, current evidence indicates that ERs are located in the nucleus[30]. Oestrogen exerts its effect by binding to ER, which after one or more molecular transformations binds to DNA, where the synthesis of mRNA is modulated.

In homogenized or steroid-depleted tissue[31], most of the receptor is found in the cytosol fraction in a 300 KDa form with a sedimentation constant of 8–9S. This consists of two molecules of a 90 kDa heat-shock (temperature-sensitive) protein, and two molecules of a 65-kDa steroid-binding protein[32]. After steroid treatment, a 5S nuclear form predominates[33,34], formed by the dissociation of both molecules of heat-shock protein. This 'activated' 5S molecule is a dimer of two molecules of the 4S, 65-kDa steroid-binding protein. Each 4S steroid-binding protein is now known to consist of two subunits of approximately 30 kDa (*Figure 1*)[35].

The ER molecule consists of six regions, denoted A–F. Each region consists of a different number of amino acids. Sequence comparisons between oestrogen[36,37], glucocorticoid[38,39] and progesterone receptors[40,41], and site-directed mutation analysis[42–44], have identified two functional domains important for ER function. Region E is the hormone-binding domain[42]. Region C is a 66-amino acid region which binds to DNA, and contains many cysteine, lysine and arginine residues[45]. Cysteine residues in this C region tetrahedrally co-ordinate zinc to form two 'zinc fingers', through which the interaction with DNA occurs[40,46–49]. The C region of ER can be subdivided into two regions, C1 and C2. It has now been shown that the oestrogen specificity of the DNA-binding domain lies in the N-terminal C1 finger[50], and three amino acids located at the C-terminal side of the ER C1 finger play a key part in this specificity[44].

The region of DNA with which the zinc fingers interact is known as the oestrogen response element. When oestrogen binds to ER the heat-shock protein is displaced and the oestrogen–ER complex becomes much more tightly bound to the nucleus. The zinc fingers bind to the oestrogen response element of the DNA, and this modulates transcription. The most obvious effect of this is on cell growth. Thus, oestrogen stimulates cell proliferation of ER-positive breast cancer cell lines[51], and probably ER-positive human tumours[52]. The mechanisms by which this occurs are still poorly understood, but the discovery of other growth factors, many of which are regulated by oestradiol, is beginning to shed light on this central issue.

Oestradiol itself is thought to regulate the number of ERs in normal breast and in tumours. Thus, higher levels of ER are seen in the first half of the menstrual cycle than in the second

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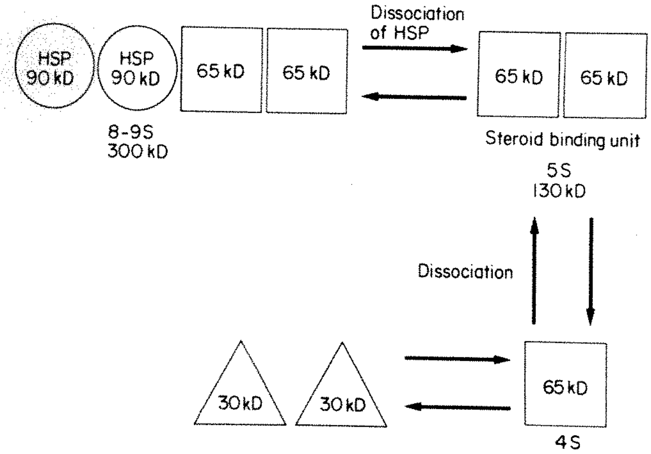

Figure 1 *Structure of the oestrogen-receptor molecule. HSP, heat-shock protein; S, Svedberg units; kDa, kilodaltons*

half[52-54], and this cyclical variation is lost in breast cancer[52]. The wide range of ER values characteristic of breast tumours is, in part, due to differences in tumour cellularity[55,56] but histochemistry has also clearly shown cell to cell heterogeneity within one tumour[57]. As in breast cancer cell lines[58], ER is probably an expression of differentiated breast cell function. A major site of regulation of ER synthesis occurs at the transcriptional level with reasonable correlations between ER levels and its RNA[59,60]. Oestradiol can regulate ER concentration by this means[61].

Progesterone receptors (PRs) are regulated by oestrogens[62]. The presence of the PR is generally coupled to functional growth regulation by oestrogens *in vivo* and *in vitro*[63]. The structure of the PR molecule is unique amongst steroid receptors. It consists of a heterodimer of two separate steroid-binding proteins (A and B) encoded by a single gene[64]. Protein A, of approximately 80 kDa, is now believed to be a truncated form of protein B, a 110-kDa protein. Both steroid-binding subunits have a sedimentation constant of 8S, and in inactivated form are probably associated with heat-shock protein. As in the ER molecule, the steroid-binding subunits have a central cysteine-rich region (region C) which co-ordinates zinc and binds to DNA. The carboxy-terminal region binds to progesterone[63].

It is interesting that human ER shares a strong sequence homology with the *v-erb A* gene of the oncogenic avian erythroblastosis virus. The *v-erb A* gene is expressed as a cytoplasmic protein of 75 kDa, which is not in itself oncogenic[65]. Instead, it appears that its action is to increase the oncogenic protential of *v-erb B* (the other cell-derived gene of avian erythroblastosis virus) which is homologous to the epidermal growth factor receptor, although it lacks the epidermal growth factor binding domain[66]. It is not clear whether this is relevant to the finding of an inverse relationship of ER with epidermal growth factor receptor which has been noted in human tumours[67].

Measurement of oestrogen receptors

There are a number of methods by which steroid receptors can be measured. The three common methods used in clinical practice for ER measurement are described. The principles are similar for measurement of PR.

Dextran-coated charcoal adsorption steroid-binding assay

This was the first and most widely used method of analysis. Quantitation of ER by the dextran-coated charcoal method will be briefly described to illustrate the principle of the method, which is described in detail elsewhere[68]. Six paired tissue cytosol aliquots of the tumour are incubated with six known concentrations of tritium-labelled oestradiol in the presence or absence of diethylstilboestrol, an unlabelled competitor for the receptor. The difference in radiolabel concentrations between non-competed and competed tubes following the removal of unbound steroid with charcoal represents specifically bound radioligand. Multipoint assays such as this allow the calculation of specific receptor content using Scatchard analysis, which is then expressed in terms of femtomoles of receptor per milligram of cytosol protein (fmol/mg). The level at which a tumour is regarded as ER negative varies with different laboratories, but is usually less than 10 fmol/mg cytosol protein.

The disadvantages of this method are that a relatively large amount of tumour tissue (about 0·5 g) is required; it is tedious and laborious to perform; and it requires the use of radioactive oestradiol and expensive equipment.

Oestrogen-receptor immunocytochemical assay (ER–ICA)

This method utilizes a monoclonal antibody (usually H222) which binds specifically to ER[30,57,69]. This technique first demonstrated that ER is situated in the nucleus[30]. Essentially, the method employs a peroxidase–antiperoxidase technique[70]. Cryostat sections of the breast tumour are lightly fixed on slides and incubated with goat serum to reduce non-specific binding. The monoclonal antibody H222 (a rat monoclonal) or control antibody (normal rat immunoglobulin) with 2 per cent normal goat serum is added dropwise and incubated. After washing, a bridging antibody (goat antirat IgG) is added dropwise and incubated. Peroxidase–antiperoxidase complex is then added to the sections which are further incubated. Specific binding is detected by the addition of the chromogen diaminobenzidine tetrahydrochloride and hydrogen peroxide. Counterstaining is then performed with Harris haematoxylin[57]. A staining intensity index can be calculated by grading the intensity of staining and counting the percentage of cells stained[57], although some workers express results in terms of the percentage of cells stained alone[71].

The advantage of this method is that no special equipment is required, very small amounts of tissue can be used, and it can even be performed on fine needle aspirates[69,72,73]. A disadvantage is that staining intensity is subjectively evaluated and this may be tedious, although it may be overcome by automating the process using video image analysis[72]. A consensus also needs to be reached on how best to express ER positivity so as to facilitate comparison of results between different centres.

Oestrogen-receptor enzyme immunoassay (ER–EIA)

The ER–EIA method is based on a sandwich technique (*Figure 2*). Breast tumour cytosols are incubated with beads coated with anti-ER monoclonal antibody. During this time, the receptor is immobilized by binding to the antibody, and unbound materials are then removed by aspiration and washing of the beads. A second ER-specific monoclonal antibody conjugated to horseradish peroxidase is added and a complex of layered antibodies and receptor is formed. The second

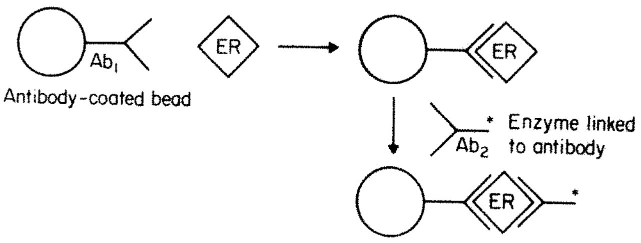

Figure 2 *Schematic representation of the oestrogen-receptor enzyme immunoassay method. Breast tumour cytosols are incubated with anti-ER antibody. A second ER-specific antibody conjugated to peroxidase is added. Addition of enzyme substrate produces a colour reaction, the intensity of which is proportional to the amount of receptor (see text). ER, oestrogen receptor; Ab, antibody; *, enzyme*

antibody recognizes a different epitope on ER. After incubation the beads are washed. The addition of substrate solution (hydrogen peroxide and *o*-phenylenediamine–2HCl) produces a colour reaction, the intensity of which is proportional to the amount of receptor present. The intensity of the colour developed is read on a spectrophotometer at 492 nm and the receptor level is determined from a standard curve of ER (human) run with the tumour cytosols[74].

The advantages of ER–EIA are that it requires less tissue than the dextran-coated charcoal method, it is quick and reliable, and it requires little special equipment. It is likely to become the standard method of quantifying ER. Several studies have concluded that very good correlations are obtained between the three methods of measurement[57,69,74] and the dextran-coated charcoal method and ER–ICA are comparable in their predictive power of response to endocrine treatment[57,69]. Fewer data, however, are available for the relationship between ER–EIA and response.

Steroid receptors in normal breast tissue

There are surprisingly few data on this topic, and it was thought that ER was absent from the normal breast. It is now known that ER is present in normal breast tissue[52–54,75,76]. Only some 7 per cent of the total cell population contains ER, and the cells are distributed as scattered single epithelial cells[75]. Using ER–ICA, it can be shown that the highest frequency and intensity of staining occurs in the lobules rather than ducts, and staining of stromal cells or myoepithelial cells is not observed[75]. Thus, ER levels in normal breast are relatively low, and are mostly confined to the first half of the menstrual cycle[52–54]. The recent observation[76] that in normal and benign breast the normal inverse relationship of ER to epidermal growth factor receptor seen in breast cancers[67] does not exist is intriguing. This suggests that there is different regulation of receptor expression in non-malignant and malignant tissue. Benign breast tumours, especially fibroadenomas, are more frequently positive for ER than normal breast tissue[77,78].

PRs have also been detected in normal human breast[79]. As with ER in normal breast tissue, levels of PR expression are relatively low, although quite high values have been found in some benign tumours, especially fibroadenomas[78,80].

Clinical correlations with steroid receptor concentrations

Overall, approximately 70 per cent of primary breast cancers are ER positive and approximately 50 per cent are PR positive[81]. Forty-six per cent of tumours are both ER and PR positive, while 23 per cent are ER and PR negative. Twenty-five per cent of tumours are ER positive and PR negative, and only 6 per cent are ER negative and PR positive[81].

The proportion of patients with ER-positive tumours increases with age[82–84]. Thus, 80 per cent of patients over the age of 60 years have ER-positive tumours, while less than 60 per cent of patients under 40 years have ER-positive tumours[82]. Although it is true that a higher proportion of postmenopausal patients have ER-positive tumours compared with premenopausal patients[82,83], this association appears to be age dependent[83]. PR expression is not affected by age or menopausal status[83,85]. The level of ER in tumours is higher in patients with a low serum oestradiol concentration[85], but this may be related to menopausal status. It is not related to the well known epidemiological risk factors of age at menarche, pregnancy, parity, oral contraceptive use, or family history[82,84]. Most studies have shown that there is no association between tumour size and ER[82,86,87]. One small study has suggested that large (T_2, T_3) tumours in postmenopausal patients express significantly higher levels of ER than small (T_1) tumours[88], but no data were given about the mean age of the two groups of postmenopausal patients. Studies on the relationship of steroid receptor expression to axillary lymph node status are conflicting. Some studies have not found a significant correlation with lymph node status[85], while others have demonstrated that lack of ER and PR is significantly associated with positive axillary nodes[89]. Body-weight is not related to ER status, although high body-weight is associated with advanced disease at presentation[90]. There is also no association of ER with breast parenchymal pattern seen on mammography[91].

The relationship of ER in primary tumours with metastases has been studied in simultaneous and sequential biopsies from the same patient. In 20–25 per cent of samples, the ER status of the metastasis was different from that of the primary tumour[92–94]. This was usually due to loss of ER expression by the metastasis, although ER-positive metastases do occur in patients in whom the primary tumour is ER negative[81]. Loss of ER expression was shown to vary with the site of metastases in one study[95]. Thus, 90 per cent of lymph node metastases had the same ER status as the primary tumour. The corresponding values for liver and bone metastases were 75 and 58 per cent respectively[95]. ER-positive tumours are more likely to metastasize to bone, whereas ER-negative tumours more commonly metastasize to the liver[95,96]. This supports the hypothesis that tumour cell clones with different ER content are selected and adapted to grow in various anatomical sites.

Similar studies performed on PR showed that up to 38 per cent of metastases had a different PR status from that of the primary tumour[93,94]. This was mostly due to greater loss of PR than ER, although for both receptors this was probably due to interference of tamoxifen in the measurement of receptor concentration[92].

Pathological correlations with ER

The pathological features associated with ER positivity are well differentiated tumours[85,97–100], slight or absent lymphoid infiltrate, slight or absent necrosis, and moderate or marked elastosis[85]. It is apparent that those tumours pathologically regarded as having a better prognosis more often express ER. Certain tumour types are also more frequently associated with ER expression such as lobular, mucinous, and tubular carcinomas, whereas comedo and medullary carcinomas rarely contain significant receptor numbers[85,101].

Tumours exhibit heterogeneity in their ER expression. Thus, intermediate areas of a tumour express more ER than central or peripheral areas of the tumour, once cellularity has been taken into account[102]. Usually there is concordance in the ER and PR classification of the different parts of the tumour[103], but a difference in receptor concentration of up to sevenfold has been reported[104]. This heterogeneity of expression is more readily observed with immunohistochemistry[57,69–71]. Studies on the influence of cellularity on ER content have been conflicting. Some studies have shown no correlation[105–108], at least in premenopausal patients[109], although other studies[107,109–111] have shown a positive correlation especially in postmenopausal patients[107].

The cell proliferation rate of tumours has now been shown to relate to adverse pathological features. Tumours with a high proliferation rate, whether measured by ploidy[112], flow cytometry[113], thymidine labelling index[114], or staining with the monoclonal antibody Ki67 which binds to a proliferation-associated antigen[115], are all associated with poorly differentiated tumours. All these indices are inversely correlated with ER expression[112–114], except for Ki67 staining, where no correlation could be demonstrated[115]. However, some studies dispute this correlation of ER with ploidy[116,117].

Steroid receptors and prognosis

The value of steroid receptors as prognostic indicators remains controversial. Several authors have concluded that patients with ER-positive tumours have a longer overall survival and disease-free survival[89,118–126]. Other studies with longer follow-up suggest that the beneficial effect of positive ER status on tumour recurrence gradually diminishes with time[89,127]. In addition, relatively few studies compare both ER and PR, and at present controversy exists as to which hormonal receptor actually conveys the favourable prognosis[118,126-130].

Eleven studies[89,118,128-136] have used multivariate analysis to assess the effect of these hormone receptors on prognosis, whilst others have relied solely on univariate analysis[96,122-125,137]. Three recent studies using multivariate analysis found that steroid receptor status was a weak prognostic factor that did not achieve statistical significance[118,130,131]. This was supported by another study of 1262 patients which concluded that PR and ER have no independent value for overall survival either at 2, 5 or 10 years[89]. This last study was complicated by the fact that all patients received some form of adjuvant chemotherapy[89]. However, the remaining studies have concluded that ER has independent prognostic significance for overall survival[128,129,132,134-136], with one exception[133]. Many of these studies have used different levels of ER and PR in deciding on steroid receptor status. It has been recently suggested that overall survival is more strongly associated with high levels of ER (>160 fmol/mg)[121]. These results are consistent with the observation that patients with ER-positive tumours have a longer survival following relapse when treated with endocrine therapy[138].

There is even less consensus on the value of steroid receptors in predicting disease-free survival. This endpoint fails to differentiate local from distant recurrences, a distinction that may affect prognosis[139]. Early results based on limited numbers of patients indicated that ER-positive patients have a longer disease-free survival than those who are ER negative[123,129,140]. Later analyses have both refuted[141-143] and confirmed[118-120] this observation. A recent study showed that PR is an independent prognostic factor for metastasis-free survival at 2 and 5 years, but loses its significance at 10 years[89]. This association seems particularly strong in patients who have received prolonged adjuvant chemotherapy[89]. In patients not receiving prolonged adjuvant treatment, ER is significantly correlated with metastasis-free survival even at 10 years[89].

It can be seen that any association between receptor status and risk of relapse is likely to be weak[144]. More important prognostic factors are tumour size, axillary node status, and growth rate of malignant cells[89,120,144,145]. In node-negative patients, measurement of steroid receptors has also mostly failed to identify those patients who relapse[96,146].

Steroid receptors and response to endocrine therapy

There is no doubt that ER status is useful in predicting response to antioestrogen therapy[57,69,96,147,148], whether ER status is assessed biochemically[96,147] or immunohistochemically[57,69,148]. Patients with ER-negative tumours have a response rate of the order of 10 per cent[96,149]. Higher response rates have been reported[147], and a strong possibility exists that the figures for ER status include false-negative results. In patients with ER-positive tumours, reported response rates vary from 32 per cent[96] to amost 80 per cent[147,148]. There are several reasons for these large variations which include the cut-off value for positive ER status, method of measurement, and interlaboratory variations. Several authors have now reported that response is related to level of expression of ER. In patients whose tumours have 'high' levels of ER (the definition of high varies from 25 to 200 fmol/mg), 60-80 per cent respond to endocrine manipulation[96,147]. These response rates are independent of menopausal status, and in controlled trials are similar to response rates for oophorectomy[150,151].

The addition of PR measurements[81] improves the predictive ability of ER measurements[152,153]. Two reviews have concluded that patients whose tumours express both ER and PR (irrespective of quantity of receptor) have response rates to endocrine therapy of approximately 70 per cent[81,154]. The response rate of tumours with neither receptor is approximately 8 per cent, while response rates of tumours which express ER or PR alone are similar at 30-40 per cent[81].

Adjuvant endocrine therapy and steroid receptors

The results of a number of clinical trials in which patients have received adjuvant tamoxifen are now available[155-161]. Patients entering most of these studies were not selected for adjuvant endocrine therapy on the basis of their receptor status except for two trials conducted by Fisher *et al.*[161,162]. Most studies have indicated that patients taking adjuvant tamoxifen gain benefit in terms of disease-free survival rates over those patients on placebo[155-158,161]. In addition, some of these studies hve shown that the patients who most benefit are those whose tumours are ER positive[156,157]. The Nolvadex® (ICI Pharmaceuticals, Macclesfield, UK) Adjuvant Trial Organisation (NATO) study[155] was the first to demonstrate a survival advantage in patients receiving adjuvant tamoxifen for 2 years, and this effect was independent of ER status. The Scottish trial[156] also reported an improvement in disease-free survival and overall survival rates for patients on tamoxifen irrespective of ER status. Both the Scottish study[156] and the Danish study[157] showed that the benefit was most marked in those patients whose tumours had ER levels above 100 fmol/mg, although the benefit was shown to occur at all levels of ER concentration, even in ER-negative patients[156]. Other subgroups of patients claimed to receive most benefit were those ER-positive patients with four or more involved axillary nodes[159].

Many of these trials are difficult to compare because of large variations in the type of patients entered into each trial. Thus, the Danish trial[157] included only postmenopausal patients, while the NATO[155], Scottish[156] and the Eastern Co-operative Group[160] studies also included premenopausal patients. Furthermore, a varying proportion of patients did not have steroid receptor levels measured. Finally, doubts have been voiced about the quality control aspect of receptor measurements in the NATO study.

The use of ER status to decide on the type of adjuvant therapy given to patients is controversial, but the results of two such trials have recently been reported[161,162]. Only one study[161] employed tamoxifen as adjuvant therapy in node-negative, ER-positive patients. After 4 years, there was no significant survival advantage in patients taking tamoxifen over placebo. However, a significant difference in disease-free survival was already observed in favour of patients taking tamoxifen. It is interesting that benefit was observed in younger (<49 years) as well as older (>50 years) women, but no comment was made on whether high levels of ER expression were more significantly associated with benefit.

In conclusion, it seems likely that all patients with early breast cancer may benefit from adjuvant tamoxifen therapy[155-157], but are more likely to do so if their tumours are receptor positive.

Conclusions

It has recently been argued that measurement of ER status need not be routinely performed[144], and these arguments have some clinical justification. It can be seen from the studies discussed that steroid receptors have some value in predicting long-term outcome. Several studies concluded that ER status is the second most important prognostic indicator after lymph node status. ER-negative tumours do seem to have a poorer long-term outcome, and in centres where tumour grade is not available ER status may be particularly helpful. ER status is useful in predicting response to endocrine therapy in advanced disease. However, a case can be made for treating metastatic disease with endocrine therapy first, without knowing the ER status, if the disease is not life threatening. It is more conventional to treat metastasic disease with chemotherapy if the primary tumour is ER negative and with endocrine therapy if the primary tumour is ER positive[163].

Should steroid receptor status be a determinant of adjuvant systemic therapy? This question is more difficult to answer. Certainly steroid receptor levels should be measured in tumours of patients entering clinical trials. The NATO[155] findings of a beneficial effect of tamoxifen in patients with ER-negative tumours requires corroboration. The role of steroid receptor measurements in patients with node-negative disease also requires further study, as it is uncertain whether steroid receptor status is the best determinant of whether patients will relapse. It is also desirable to know the receptor status of tumours in patients undergoing primary medical therapy rather than surgery because it allows a rational choice to be made between endocrine therapy and cytotoxic chemotherapy[148,164]. The development of immunocytochemical assays will allow study of the effect of therapy on receptor levels in individual patients.

Probably of more importance, research into the details of the ER mechanism may shed further light on the pathophysiological aspects of mammary cell growth. This may lead to therapeutic strategies that will extend to routine patient management.

References

1. Henderson BE, Ross R, Bernstein L. Estrogens as a cause of human cancer: The Richard and Hinda Rosenthal Foundation award lecture. *Cancer Res* 1988; **48**: 246–53.
2. Beatson GT. On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment with illustrative cases. *Lancet* 1896; **ii**: 104–7.
3. Boyd S. On oophorectomy in cancer of the breast. *Br Med J* 1900; **ii**: 1161–7.
4. Katzenellenbogen BS, Kendra KL, Norman KN, Berthois Y. Proliferation, hormonal responsiveness and estrogen-receptor content of MCF-7 human breast cancer cells grown in the short-term and long-term absence of estrogen. *Cancer Res* 1987; **47**: 4355–60.
5. Jensen EV, Suzuki T, Kawashima T *et al.* A two-step mechanism for the interaction of estradiol with rat uterus. *Proc Natl Acad Sci USA* 1968; **59**: 632–8.
6. Eppenberger U. New aspects of the molecular growth regulation of mammary tumours. In: Eppenberger U, Goldhirsch A, eds. *Endocrine Therapy and Growth Regulation of Breast Cancer. Recent Results Cancer Res* 1989, Berlin–Heidelberg: Springer-Verlag. Vol 113: 1–3.
7. Lippman ME, Dickson RB. Mechanisms of growth control in normal and malignant breast epithelium. *Recent Prog Horm Res* 1989; **45**: 383–440.
8. Goustin AS, Leof EB, Shipley GD, Moses HL. Growth factors and cancer. *Cancer Res* 1986; **46**: 1015–29.
9. Lippman ME, Dickson RB, Gelmann EP *et al.* Human breast carcinoma cells produce growth regulatory peptides. In: Brescioni F, King RJB, Lippman ME, Raynaud J-P, eds. *Progress in Cancer Research and Therapy, Vol. 35. Hormones and Cancer 3.* New York: Rowen Press, 1988: 203–13.
10. Lippman ME. Definition of hormones and growth factors required for optimal proliferation and expression of phenotypic responses in human breast cancer cells. In: Barnes DW, Sirbasku DA, Sato GH, eds. *Cell Culture Methods for Molecular and Cell Biology*, Vol. 2. New York: Alan R Liss, 1984: 183–200.
11. Ikeda T, Sirbasku DA. Purification and properties of a mammary–uterine–pituitary tumour cell growth factor from pregnant sheep uterus. *J Biol Chem* 1984; **259**: 4049–64.
12. Dickson RB, Bates SE, McManaway ME, Lippman ME. Characterization of estrogen responsive transforming activity in human breast cancer cell lines. *Cancer Res* 1986; **46**: 1707–13.
13. Butler WB, Kirkland WL, Jorgensen TL. Induction of plasminogen activator by estrogen in a human breast cancer cell line (MCF-7). *Biochem Biophys Res Commun* 1979; **90**: 1328–34.
14. Osborne CK, Hobbs K, Clark GM. Effect of estrogens and antiestrogens on growth of human breast cancer cells in athymic nude mice. *Cancer Res* 1985; **45**: 584–90.
15. Dickson RB, Lippman ME. Estrogenic regulation of growth and polypeptide growth factor secretion in human breast carcinoma. *Endocr Rev* 1987; **8**: 29–43.
16. Bronzert DA, Pantazis P, Antoniades HN *et al.* Synthesis and secretion of platelet derived growth factor by human breast cancer cell lines. *Proc Natl Acad Sci USA* 1987; **84**: 5763–7.
17. Dickson RB, Huff KK, Spencer EM, Lippman ME. Induction of epidermal growth factor-related polypeptides by 17 estradiol in human breast cancer cells. *Endocrinology* 1985; **118**: 138–42.
18. Pekonen F, Partanen S, Makinen T, Rutanen E-M. Receptors for epidermal growth factor and insulin-like growth factor I and their relation to steroid receptors in human breast cancer. *Cancer Res* 1988; **48**: 1343–7.
19. Gregory H, Thomas CE, Willshire IR *et al.* Epidermal and transforming growth factor-α in patients with breast tumours. *Br J Cancer* 1989; **59**: 605–9.
20. Heldin CH, Westermark B. Growth factors: mechanism of action and relation to oncogenes. *Cell* 1984; **37**: 9–20.
21. Turkington RW. Stimulation of mammary carcinoma cell proliferation by epidermal growth factor *in vitro*. *Cancer Res* 1969; **29**: 1457–8.
22. Nishizuka, Y. The role of protein kinase C in cell surface signal transduction and tumour promotion. *Nature* 1984; **308**: 693–8.
23. Edwards DP, Adams DJ, McGuire WL. Estradiol stimulates synthesis of a major intracellular protein in a human breast cancer cell line (MCF-7). *Breast Cancer Res Treat* 1981; **1**: 209–23.
24. Edwards DP, Adams DJ, Savage N, McGuire WL. Estrogen-induced synthesis of a major intracellular protein in human breast cancer cells. *Biochem Biophys Res Commun* 1980; **93**: 804–12.
25. Rayter Z. Glycoproteins in squamous and breast carcinoma. *MS thesis*, University of London, 1988.
26. Rochefort H, Capony F, Chalbos D *et al.* The action of oestrogens and antioestrogens on cultured breast tumour cell lines. *Br J Cancer* 1984; **49**: 379–80.
27. Westley B, May FEB, Brown AMC *et al.* Effects of antiestrogens on the estrogen-regulated p52 RNA and the 52- and 160-kilodalton proteins in MCF-7 cells and two tamoxifen-resistant sublines. *J Biol Chem* 1984; **259**: 10 030–5.
28. Spyratos F, Mandelonde T, Brouillet J-P *et al.* Cathepsin D: an independent prognostic factor for metastasis in breast cancer. *Lancet* 1989; **ii**: 1115–18.
29. Jensen EV, de Sombre ER. Estrogen receptor interaction. *Science* 1973; **18**: 126–34.
30. King WJ, Greene GL. Monoclonal antibodies localize oestrogen receptor in the nuclei of target cells. *Nature* 1984; **307**: 745–7.
31. Redeuilh G, Moncharmont B, Secco C, Baulieu E-E. Subunit composition of the molybdate-stabilised '8-9S' nontransformed estradiol receptor purified from calf uterus. *J Biol Chem* 1987; **262**: 6969–75.
32. Schuh S, Yonemoto W, Brugge J *et al.* A 90 000-dalton binding protein common to both steroid receptors and the Rous sarcoma virus transforming protein p p $60^{v\ src}$. *J Biol Chem* 1985; **260**: 14 292–6.
33. Notides AC. Conformational forms of the estrogen receptor. In: O'Malley BW, Birnbaumer L, eds. *Receptors and Hormone Action*, Vol. 2. New York: Academic Press, 1978: 33–40.
34. Miller MA, Mullick A, Greene GL, Katzenellenbogen BS. Characterisation of the subunit nature of nuclear estrogen receptors by chemical cross-linking and dense amino acid labelling. *Endocrinology* 1985; **117**: 515–22.
35. Sabbah M, Redeuilh G, Baulieu E-E. Subunit composition of the estrogen receptor. *J Biol Chem* 1989; **264**: 2397–400.
36. Krust A, Green S, Argos P *et al.* The chicken oestrogen receptor sequence: homology with *v-erb A* and the human oestrogen and glucocorticoid receptors. *EMBO J* 1986; **5**: 891–7.
37. Green S, Walter P, Kumar V *et al.* Human oestrogen receptor with DNA: sequence, expression and homology to *v-erb A*. *Nature* 1986; **320**: 134–9.
38. Hollenberg SM, Weinberger C, Ong ES *et al.* Primary structure and expression of a functional human glucocorticoid receptor with DNA. *Nature* 1985; **318**: 635–41.
39. Miesfeld R, Rusconi S, Godowski PJ *et al.* Genetic complementation of a glucocorticoid receptor deficiency by expression of cloned receptor cDNA. *Cell* 1986; **46**: 389–99.
40. Jeltsch JM, Krozowski Z, Quirin-Stricker P *et al.* Cloning of the chicken progesterone receptor. *Proc Natl Acad Sci USA* 1986; **83**: 5424–8.
41. Conneely OM, Sullivan WP, Toft DO *et al.* Molecular cloning of the chicken progesterone receptor. *Science* 1986; **233**: 767–70.
42. Kumar V, Green S, Staub A, Chambon P. Localisation of the oestradiol-binding and putative DNA-binding domains of the human oestrogen receptor. *EMBO J* 1986; **5**: 2231–6.
43. Giguere V, Hollenberg SM, Rosenfeld MG, Evans RM.

Functional domains of the human glucocorticoid receptor. *Cell* 1986; **46**: 645–52.

44. Mader S, Kumar V, de Verneuil H, Chambon P. Three amino acids of the oestrogen receptor are essential to its ability to distinguish an oestrogen from a glucocorticoid responsive element. *Nature* 1989; **338**: 271–4.
45. Green S, Chambon P. Oestradiol induction of a glucocorticoid-responsive gene by a chimaeric receptor. *Nature* 1987; **325**: 75–8.
46. Miller J, McLachlan AD, Klug A. Repetitive zinc-binding domains in the protein transcription factor IIIA from *Xenopus* oocytes. *EMBO J* 1985; **4**: 1609–14.
47. Hartshorne TA, Blumberg H, Young ET. Sequence homology of the yeast regulatory protein ADR 1 with *Xenopus* transcription factor TFIIIA. *Nature* 1986; **320**: 283.
48. Green S, Chambon P. Nuclear receptors enhance our understanding of transcription regulation. *Trends In Genetics* 1988; **4**: 309–14.
49. Ponglikitmongkol M, Green S, Chambon P. Genomic organization of the human oestrogen receptor gene. *EMBO J* 1988; **7**: 3385–8.
50. Green S, Kumar V, Theulaz L, Wahl W, Chambon P. The N-terminal DNA-binding 'zinc finger' of the oestrogen and glucocorticoid receptors determines target gene specificity. *EMBO J* 1988; **7**: 3037–44.
51. Darbre PD, Glover JF, King RJB. Effects of steroids and their antagonists on breast cancer cells: therapeutic implications. *Recent Results Cancer Res* 1989; **113**: 16–28.
52. Markopolous C, Berger U, Wilson P, Gazet J-C, Coombes RC. Oestrogen receptor content of normal breast cells and breast carcinoma throughout the menstrual cycle. *Br Med J* 1988; **296**: 1349–51.
53. Anderson TJ, Battersby S. The involvement of oestrogen in the development and function of the normal human breast: histological evidence. *Proc R Soc Edinb* 1989; **95B**: 23–32.
54. Carpenter S, Georgiade G, McCarty KS Sr, McCarty KS Jr. Immunohistochemical expression of oestrogen receptor in normal breast tissue. *Proc R Soc Edinb* 1989; **95B**: 59–66.
55. Black R, Prescott R, Bers K *et al.* Tumour cellularity, oestrogen receptors and prognosis in breast cancer. *Clin Oncol* 1983; **9**: 311–18.
56. Mumford CJ, Elston CW, Campbell FC *et al.* Tumour epithelial cellularity and quantitative oestrogen receptor values in primary breast cancer. *Br J Cancer* 1983; **47**: 549–52.
57. McClelland RA, Berger U, Miller LS *et al.* Immunocytochemical assay for estrogen receptor: relationship to outcome of therapy in patients with advanced breast cancer. *Cancer Res* 1986; **46**(Suppl): 4241s–3s.
58. Engel LW, Young NA. Human breast carcinoma cells in continuous culture: a review. *Cancer Res* 1978; **38**: 4327–39.
59. Barrett-Lee PJ, Travers MT, McClelland RA, Luqmani Y, Coombes RC. Characterization of estrogen receptor messenger RNA in human breast cancer. *Cancer Res* 1987; **47**: 6653–9.
60. Garcia T, Lehrer S, Bloomer WD, Schacter B. A variant estrogen receptor messenger ribonucleic acid is associated with reduced levels of estrogen binding in human mammary tumours. *Mol Endocrinol* 1988; **2**: 785–91.
61. Piva R, Bianchini E, Kumar VL, Chambon P, del Senno L. Oestrogen-induced increase of oestrogen receptor RNA in human breast cancer cells. *Biochem Biophys Res Commun* 1988; **155**: 943–9.
62. Horwitz KB, McGuire WL. Estrogen control of progesterone receptor in human breast cancer. *J Biol Chem* 1978; **253**: 223–8.
63. Savouret JF, Misrahi M, Loosfelt H *et al.* Molecular and cellular biology of mammalian progesterone receptors. *Recent Prog Horm Res* 1989; **45**: 65–111.
64. Krett NL, Wei LL, Francis MD *et al.* Human progesterone A-receptors can be synthesized intracellularly and are biologically functional. *Biochem Biophys Res Commun* 1988; **157**: 278–85.
65. Frykberg L, Palmieri S, Berg H *et al.* Transforming capacities of avian erythroblastosis virus mutants deleted in the *erb A* or *erb B* oncogenes. *Cell* 1983; **32**: 227–38.
66. Ullrich A, Coussens L, Hayflick JS *et al.* Human epidermal growth factor receptor cDNA sequence and aberrant expression of the amplified gene in A 431 epidermoid carcinoma cells. *Nature* 1984; **309**: 418–25.
67. Sainsbury JRC, Farndon JR, Sherbet GV, Harris AL. Epidermal growth factor receptors and oestrogen receptors in human breast cancers. *Lancet* 1985; **i**: 364–6.
68. McGuire WL, de la Garza M. Improved sensitivity in the measurement of estrogen receptor in human breast cancer. *J Clin Endocrinol Metab* 1973; **37**: 986–9.
69. Hawkins RA, Sangster K, Tesdale A *et al.* The cytochemical detection of oestrogen receptors in fine needle aspirates of breast cancer; correlation with biochemical assay and prediction of response to endocrine therapy. *Br J Cancer* 1988; **58**: 77–80.
70. Press MF, Greene GL. An immunocytochemical method for demonstrating oestrogen receptor in human uterus using monoclonal antibodies to human estrophilin. *Lab Invest* 1984; **50**: 480–6.
71. Walker KJ, Bouzubar N, Robertson J *et al.* Immunocytochemical localization of estrogen receptor in human breast tissue. *Cancer Res* 1988; **48**: 6517–22.
72. Horsfall DJ, Jarvis LR, Grimbaldeston MA, Tilley WD, Orell SR. Immunocytochemical assay for oestrogen receptor in fine needle aspirates of breast cancer by video image analysis. *Br J Cancer* 1989; **59**: 129–34.
73. Marrazzo A, la Bara G, Taormina P, Bazan P. Determination of oestrogen receptors with monoclonal antibodies in fine needle aspirates of breast carcinoma. *Br J Cancer* 1989; **59**: 426–8.
74. Jordan VC, Jacobson HI, Keenan EJ. Determination of estrogen receptor in breast cancer using monoclonal antibody technology: result of a multicentre study in the United States. *Cancer Res* 1986; **46**(Suppl): 4237s–40s.
75. Peterson OW, Hoyer PE, van Deurs B. Frequency and distribution of estrogen receptor-positive cells in normal, non-lactating human breast tissue. *Cancer Res* 1987; **47**: 5748–51.
76. Barker S, Pomahy C, Puddefoot JR, Goode AW, Vinson GP. Epidermal growth factor receptor and oestrogen receptors in the non-malignant part of the cancerous breast. *Br J Cancer* 1989; **60**: 673–7.
77. Allegra J, Lippman ME, Green L *et al.* Estrogen receptor values in patients with benign breast disease. *Cancer* 1979; **44**: 228–31.
78. Giani C, d'Amore E, Delarue JC *et al.* Estrogen and progesterone receptors in benign breast tumours and lesions: relationship with histological and cytological features. *Int J Cancer* 1986; **37**: 7–10.
79. Silva JS, Georgiade GS, Dilley WG *et al.* Menstrual cycle-dependent variations of breast cyst fluid proteins and sex steroid receptors in the normal human breast. *Cancer* 1983; **51**: 1297–302.
80. Martin PM, Kutten F, Serment H, Mauvais-Jarvis P. Progesterone receptors in breast fibroadenomas. *J Steroid Biochem* 1979; **11**: 1295–8.
81. Kvinnsland S. Steroid receptor assay and prognosis. In: Stoll BA, ed. *Breast Cancer: Treatment and Prognosis.* Oxford: Blackwell Scientific Publications, 1986: 140–54.
82. Elwood JM, Godolphin W. Oestrogen receptors in breast tumours: associations with age, menopausal status and epidemiological and clinical features in 735 patients. *Br J Cancer* 1980; **42**: 635–44.
83. Helin HJ, Isola JJ, Helle MJ, Aldercrentz H. Influence of endocrine status on bichemical and immunocytochemical estrogen and progesterone receptor assays in breast cancer patients. *Breast Cancer Res Treat* 1988; **12**: 67–73.
84. Cooper JA, Rohan TE, Cant ELMcK, Horsfall DJ, Tilley WD. Risk actors for breast cancer by oestrogen receptor status: a population-based case–control study. *Br J Cancer* 1989; **59**: 119–25.
85. Fisher ER, Sass R, Fisher B. Pathologic findings from the National Surgical Adjuvant Breast Project. Correlations with concordant and discordant estrogen and progesterone receptors. *Cancer* 1987; **59**: 1554–9.
86. Rozen PP, Menendez-Botel CJ, Nisselbaum JS *et al.* Pathological review of breast lesions analyzed for estrogen receptor protein. *Cancer Res* 1975; **35**: 3187–94.
87. Mason BH, Holdaway IM, Mullins PR *et al.* Progesterone and estrogen receptors as prognostic variables in breast cancer. *Cancer Res* 1983; **43**: 2985–90.
88. Kaplan O, Skornick Y, Greif F, Klausner Y, Rozin RR. A correlation between oestrogen receptors and tumour size in primary breast cancer. *Eur J Surg Oncol* 1985; **11**: 357–60.
89. Spyratos F, Hacene K, Tubiana-Hulin M, Pallud Cl, Brunet M. Prognostic value of estrogen and progesterone receptors in primary infiltrating ductal breast cancer. A sequential multivariate analysis of 1262 patients. *Eur J Cancer Clin Oncol* 1989; **25**: 1233–40.
90. Williams G, Howell A, Jones M. The relationship of body weight to response to endocrine therapy, steroid hormone receptors

and survival of patients with advanced cancer of the breast. *Br J Cancer* 1988; **58**: 631–4.

91. Ciatto S, Cecchini S, Iossan A *et al.* Association of oestrogen receptors with parenchymal pattern at mammography. *Radiology* 1989; **170**: 695–7.
92. Hull DF III, Glark GM, Osborne CK *et al.* Multiple estrogen receptor assays in human breast cancer. *Cancer Res* 1983; **43**: 413–16.
93. Klinga K, Kaufmann M, Runnebaum B, Kubli F. Distribution of oestrogen and progesterone receptors on primary and lymph nodes in individual patients with breast cancer. *Oncology* 1982; **39**: 337–9.
94. Lee Y-TN. Variability of steroid receptors in multiple biopsies of breast cancer: effect of systemic therapy. *Breast Cancer Res Treat* 1982; **2**: 185–93.
95. Kamby C, Rasmussen RB, Kristensen B. Oestrogen receptor status of primary breast carcinomas and their metastases. Relation to pattern of spread and survival after first recurrence. *Br J Cancer* 1989; **60**: 252–7.
96. Williams MR, Todd JH, Ellis IO *et al.* Oestrogen receptors in primary and advanced breast cancer: an eight year review of 704 cases. *Br J Cancer* 1987; **55**: 67–73.
97. Fisher ER, Redmond CK, Liu H, Rockette H, Fisher B. Correlation of estrogen receptor and pathologic characteristics of invasive breast cancer. *Cancer* 1980; **45**: 349–53.
98. Fisher ER, Osborne CK, McGuire WL *et al.* Correlation of primary breast cancer histopathology and estrogen receptor content. *Breast Cancer Res Treat* 1981; **1**: 37–41.
99. Kamby C, Anderson J, Ejlertson B *et al.* Histological grade and steroid receptor content of primary breast cancer – impact on prognosis and possible modes of action. *Br J Cancer* 1988; **58**: 480–6.
100. Singh L, Wilson AJ, Baum M *et al.* The relationship between histological grade, oestrogen receptor status, events and survival at 8 years in the NATO (Nolvadex) trial. *Br J Cancer* 1988; **57**: 612–14.
101. Helin HJ, Helle MJ, Kallioneimi O-P, Isola JJ. Immunohistochemical determination of estrogen and progesterone receptors in human breast carcinoma. *Cancer* 1989; **63**: 1761–7.
102. Van Netten JP, Armstrong JB, Carlyle SS *et al.* Oestrogen receptor distribution in the peripheral, intermediate and central regions of breast cancers. *Eur J Cancer Clin Oncol* 1988; **24**: 1885–9.
103. Braunsberg H. Factors influencing the estimation of oestrogen receptors in human malignant breast tumours. *Eur J Cancer* 1975; **14**: 1337–40.
104. Hawkins RA, Roberts MM, Forrest AP. Oestrogen receptors and breast cancer: current status. *Br J Surg* 1980; **67**: 153–69.
105. Feherty P, Farrar-Brown C, Kellie AG. Oestradiol receptors in carcinoma and benign disease of the breast: an *in vitro* assay. *Br J Cancer* 1971; **25**: 697–710.
106. Wittliff JI, Hilf R, Brooks WF *et al.* Specific estrogen binding capacity of the cytoplasmic receptor in normal and neoplastic breast tissues of humans. *Cancer Res* 1972; **32**: 1983–92.
107. Mumford CJ, Elston CW, Campbell FC *et al.* Tumour epithelial cellularity and quantitative oestrogen receptor values in primary breast cancer. *Br J Cancer* 1983; **47**: 549–52.
108. Parham DM, Baker PR, Robertson AJ *et al.* Breast carcinoma cellularity and its relation to oestrogen receptor content. *J Clin Pathol* 1989; **42**: 1166–8.
109. Terenius L, Johansson H, Rimsten A, Thoren L. Malignant and benign mammary disease: estrogen binding in relation to clinical data. *Cancer* 1974; **33**: 1364–8.
110. Masters JRW, Hawkins RA, Sangster K *et al.* Oestrogen receptors, cellularity, elastosis and menstrual status in human breast cancer. *Eur J Cancer* 1978; **14**: 303–7.
111. Hawkins RA, Killen E, Tesdale AL *et al.* Oestrogen receptors, lactate dehydrogenase and cellularity in human breast cancer. *Clin Chim Acta* 1988; **175**: 89–96.
112. Stal O, Wingren S, Carstensen J *et al.* Prognostic value of DNA ploidy and S-phase fraction in relation to oestrogen receptor content and clinicopathological variables in primary breast cancer. *Eur J Cancer Clin Oncol* 1989; **25**: 301–9.
113. Kute T, Muss HB, Hopkins M *et al.* Relationship of flow cytometry results to clinical and steroid receptor status in human breast cancer. *Breast Cancer Res Treat* 1985; **6**: 113–21.
114. Meyer J, Rao BR, Stevens SC, White WL. Low incidence of estrogen receptor in breast carcinomas with rapid rates of cellular replication. *Cancer* 1977; **40**: 2290–8.
115. Bouzubar N, Walker KJ, Griffiths K *et al.* Ki 67 immunostaining in primary breast cancer: pathological and clinical associations. *Br J Cancer* 1989; **59**: 943–7.
116. Fossa SD, Thorud E, Shoaib MC *et al.* DNA flow cytometry in primary breast carcinoma. *APMIS Sect A* 1984; **92**: 475–80.
117. Taylor IW, Musgrove EA, Friedlander ML, Foo MS, Hedley DW. The influence of age on the DNA ploidy levels of breast tumours. *Eur J Oncol* 1983; **19**: 623–8.
118. Sutton R, Campbell M, Cooke T *et al.* Predictive power of progesterone receptor status in early breast carcinoma. *Br J Surg* 1987; **74**: 223–6.
119. Hawkins RA, White G, Bundred NJ *et al.* Prognostic significance of oestrogen and progesterone receptor activities in breast cancer. *Br J Surg* 1987; **74**: 1009–13.
120. Chevalier B, Heintzmann F, Mosseri V *et al.* Prognostic value of estrogen and progesterone receptors in operable breast cancer. *Cancer* 1988; **62**: 2517–24.
121. Shek LL, Godolphin W. Survival with breast cancer: the importance of estrogen receptor quantity. *Eur J Cancer Clin Oncol* 1989; **25**: 243–50.
122. Raemakers JMM, Beex LV, Koenders AJM *et al.* Disease free interval and estrogen receptor activity in tumour tissue of patients with primary breast cancer: analysis after long-term follow up. *Breast Cancer Res Treat* 1985; **6**: 123–30.
123. Knight WA, Livingstone RB, Gregory EJ *et al.* Estrogen receptor as an independent prognostic factor for early recurrence in breast cancer. *Cancer Res* 1977; **37**: 4669–71.
124. Park FF, Schmidt BP, Dupont WD, Wagner R. Prognostic significance of estrogen receptor status in breast cancer in relation to tumour stage, axillary node metastases and histological grading. *Cancer* 1984; **54**: 2237–42.
125. Godolphin W, Elwood JM, Spinelli JJ. Estrogen receptor quantification and staging as complementary prognosis indicators in breast cancer. A study of 583 patients. *Int J Cancer* 1981; **28**: 677–83.
126. Mason BH, Holdaway IM, Mullins PR, Yee LH, Kay RG. Progesterone and estrogen receptors as prognostic variables in breast cancer. *Cancer Res* 1983; **43**: 2985–90.
127. Howat JM, Barnes DM, Harris M, Swindell R. The association of cytosol oestrogen and progesterone receptors with histological features of breast cancer and early recurrence of disease. *Br J Cancer* 1983; **47**: 629–40.
128. Stewart JF, Rubens RD, Millis RR, King RJB, Hayward J. Steroid receptors and prognosis in operable (stage I and II) breast cancer. *Eur J Cancer Clin Oncol* 1983; **19**: 1381–7.
129. McGuire WL, Clark GM, Dressler LG, Owens M. Role of steroid hormone receptors as prognostic factors in primary breast cancer. *NCI Monogr* 1986; **i**: 19–23.
130. Caldarola L, Volterani P, Caldarola B *et al.* The influence of hormone receptors and hormonal adjuvant therapy on disease free survival in breast cancer: a multifactorial analysis. *Eur J Cancer Clin Oncol* 1986; **22**: 151–5.
131. Todd JH, Dowle GL, Williams MR *et al.* Confirmation of a prognostic index in primary breast cancer. *Br J Cancer* 1987; **56**: 482–92.
132. Alanko A, Heinonen E, Scheinin T, Tolppanen E-M, Vihko R. Significance of estrogen and progesterone receptors, disease-free interval and site of first metastasis on survival of breast cancer patients. *Cancer* 1985; **56**: 1696–700.
133. Hatschek T, Carstensen J, Fagerberg C *et al.* Influence of S-phase fraction on metastatic pattern and post-recurrence survival in a randomized mammography screening trial. *Breast Cancer Res Treat* 1989; **14**: 321–7.
134. Bryan RM, Mercer RJ, Bennett RC, Ritchie GC. Prognostic factors in breast cancer and the development of a prognostic index. *Br J Surg* 1986; **73**: 267–71.
135. Thor A, Schwartz LH, Koerner FC *et al.* Analysis of *c-erb B-2* expression in breast carcinomas with clinical follow-up. *Cancer Res* 1989; **49**: 7147–52.
136. Marques LA, Franco E, Torloni H *et al.* Independent prognostic value of laminin receptor expression in breast cancer survival. *Cancer Res* 1990; **50**: 1479–83.
137. Adami HO, Graffman S, Lindgren A, Sallstrom J. Prognostic implication of estrogen receptor content in breast cancer. *Breast Cancer Res Treat* 1985; **5**: 293–300.
138. Howell A, Barnes DM, Harland RN *et al.* Steroid hormone receptors and survival after first relapse in breast cancer. *Lancet* 1984; **i**: 588–91.
139. Bedwinek JM, Lee J, Fineberg B, Ocwieza M. Prognostic indicators in patients with isolated locoregional recurrence of breast cancer. *Cancer* 1981; **47**: 2232–5.

140. Cooke T, George D, Shields R, Maynard P, Griffiths K. Oestrogen receptors and prognosis in early breast cancer. *Lancet* 1979; **i**: 995–7.
141. Skinner JR, Warnebo JH, Betshill WC *et al.* Evaluation of the pathologic and prognostic correlates of estrogen receptors in primary breast cancer. *Ann Surg* 1982; **196**: 636–41.
142. Blamey RW, Bishop HM, Blake JRS *et al.* Relationship between primary breast tumour receptor status and patient survival. *Cancer* 1980; **46**: 2765–9.
143. Saez S, Cheix F, Asselain B. Prognostic value of estrogen and progesterone receptors in primary breast cancer. *Breast Cancer Res Treat* 1983; **3**: 345–54.
144. Barnes DM, Fentiman IS, Millis RR, Rubens RD. Who needs steroid receptor assays? *Lancet* 1989; **i**: 1126–7.
145. van Rosen A, Rutqvist LE, Carstensen J *et al.* Prognostic value of nuclear DNA content in breast cancer in relation to tumour size, nodal status, and estrogen receptor content. *Breast Cancer Res Treat* 1989; **13**: 23–32.
146. Maki HS, Hoehn JL. The influence of estrogen receptors on survival and recurrence in patients with breast cancer without lymph node metastases. *Arch Surg* 1989; **124**: 377–80.
147. Oriani S, Bohm S, Baeli A *et al.* Clinical response and survival according to oestrogen receptor levels after bilateral ovariectomy in advanced breast cancer. *Eur J Surg Oncol* 1989; **15**: 39–42.
148. Gaskell DJ, Hawkins RA, Sangsterl K, Chetty U, Forrest APM. Relation between immunocytochemical estimation of oestrogen receptor in elderly patients with primary breast cancer and response to tamoxifen. *Lancet* 1989; **i**: 1044–6.
149. de Sombre ER, Greene GL, Jensen EV. Estrogen receptors and hormone dependence of breast cancer. In: Brennan MJ, McGrath CM, Rich MA, eds. *Breast Cancer: New Concepts in Etiology and Control*. New York: Academic Press, 1980: 69.
150. Buchanan RB, Blamey RW, Durrant KR *et al.* A randomized comparison of tamoxifen with surgical oophorectomy in premenopausal patients with advanced breast cancer. *J Clin Oncol* 1986; **4**: 1326–30.
151. Ingle JN, Krook JE, Green SJ *et al.* Randomized trial of bilateral oophorectomy *versus* tamoxifen in premenopausal women with metastatic breast cancer. *J Clin Oncol* 1986; **4**: 178–85.
152. Clark GM, McGuire WL. Progesterone receptors and human breast cancer. *Breast Cancer Res Treat* 1983; **3**: 157–63.
153. Horwitz KB, McGuire WL, Pearson OH, Segaloff A. Predicting response to endocrine therapy in human breast cancer: a hypothesis. *Science* 1975; **189**: 726–7.
154. Hawkins RA. Receptors in the management of breast cancer. *Br J Hosp Med* 1985; **34**: 160–4.
155. Nolvadex Adjuvant Trial Organisation. Controlled trial of tamoxifen as single adjuvant agent in management of early breast cancer. *Lancet* 1985; **i**: 836–40.
156. Breast Cancer Trials Committee, Scottish Cancer Trials Office. Adjuvant tamoxifen in the management of operable breast cancer: the Scottish trial. *Lancet* 1987; **ii**: 171–5.
157. Rose C, Thorpe SM, Anderson KW *et al.* Beneficial effect of adjuvant tamoxifen therapy in primary breast cancer patients with high oestrogen receptor levels. *Lancet* 1985; **i**: 16–19.
158. Ludwig Breast Cancer Study Group. Randomized trial of chemo-endocrine therapy, endocrine therapy, and mastectomy alone in postmenopausal patients with operable breast cancer and axillary node metastases. *Lancet* 1984; **i**: 1256–460.
159. Hubay CA, Gordon NH, Crowe JP *et al.* Antiestrogen-cytotoxic chemotherapy and bacillus Calmette–Guerin vaccination in stage II breast cancer: seventy-two month follow-up. *Surgery* 1984; **96**: 61–72.
160. Tormey DC, Kalish L, Cummings FJ, Carbonne PP. Premenopausal breast cancer adjuvant chemotherapy – the Eastern Cooperative Oncology Group Trial. *Proc Am Soc Clin Oncol* 1983; **2**: 102.
161. Fisher B, Constantino J, Redmond C *et al.* A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumours. *N Engl J Med* 1989; **320**: 479–84.
162. Fisher B, Redmond C, Dimitrou NV *et al.* A randomized clinical trial evaluating sequential methotrexate and fluorouracil in the treatment of patients with node-negative breast cancer who have estrogen-receptor-negative tumours. *N Engl J Med* 1989; **320**: 473–8.
163. Henderson IC. The treatment of advanced breast cancer. *Rec Adv Clin Oncol* 1986; **2**: 135–56.
164. Rayter Z, Phipps R. Primary medical treatment in breast cancer. *BMJ* 1991; **302**: 2–3.

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Hereditary sacral agenesis with presacral mass and anorectal stenosis: the Currarino triad

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A family with autosomal dominant inheritance of sacral agenesis is described. Ten members were affected; four had associated presacral teratomas and anterior sacral meningoceles, giving rise to serious complications in three, including bacterial meningitis, local recurrence of teratoma and perianal sepsis. Three of those with presacral masses presented initially with anorectal anomalies. Other associated abnormalities included tethering of the cord, hydrocephalus, duplex ureter, hydronephrosis, vesicoureteric reflux, neurogenic bladder, bicornuate uterus, rectovaginal fistula and hereditary spherocytosis. Early diagnosis and surgical excision of a presacral mass is advised to prevent future morbidity and mortality.

Sacral agenesis, the congenital absence of whole or part of the sacrum, is rare. Its association with a presacral mass and congenital anorectal stenosis was described in 1981 by Currarino *et al.*[1]. We extend a previous report[2] of a family with autosomal dominant inheritance of sacral agenesis and provide a further 15 years of follow-up. Ten members of the family had congenital sacral agenesis. Four had a presacral mass, which gave rise to serious complications in three cases. Three had the complete Currarino triad.

Family and patients

The family pedigree is set out in *Figure 1*. Four family members merit detailed discussion.

Case 1 (III 4, Figure 1)

A 25-year-old woman had constipation and soiling from birth. A large rectovaginal fistula was diagnosed at the age of 30 months and was subsequently repaired. Sacral agenesis was diagnosed radiologically. Persistent soiling led to permanent colostomy at the age of 7 years. The patient re-presented with recurrent perianal sepsis 13 years later. A sinus tract in the lateral rectal wall and a presacral mass 5 cm in diameter were found. Myelography revealed a presacral meningocele 1·5 cm in diameter. Abdominoperineal excision of the rectal stump and presacral mass was undertaken. At operation the mass was found to communicate with the rectum but not with the subarachnoid space and no separate sacral meningocele was identified. An uncomplicated postoperative recovery ensued. The histological findings were those of a benign cystic teratoma. Associated abnormalities in this case included hereditary spherocytosis, ovarian cystadenoma and bicornuate uterus.

Case 2 (III 5, Figure 1)

A 24-year-old woman had sacral agenesis (*Figure 2*). Examination at the age of 7 years had revealed a small soft presacral tumour. She was asymptomatic and was not offered surgery. She remained asymptomatic and at the age of 24 years was invited for further evaluation. On rectal examination a presacral mass was palpable. Computed tomographic myelography demonstrated a presacral cyst 12 cm in diameter which communicated with the subarachnoid space, and a diagnosis of anterior sacral meningocele was made (*Figure 3*). At laparotomy the cyst, which communicated through the anterior wall of the sacrum with the spinal canal, did not contain neural tissue and was distinct from the rectum. A subseptate uterus was noted. The mass was excised and the patient made an uncomplicated recovery. Histological examination revealed a benign cystic teratoma.

Case 3 (III 6, Figure 1)

This patient presented with soiling at the age of 2 years. Anal stenosis, sacral agenesis and a presacral mass were diagnosed. A benign presacral teratoma was excised but recurred locally within 1 year, necessitating abdominoperineal excision of the rectum and associated mass. Six months later an inoperable brain stem tumour was diagnosed and the patient died at 4 years of age. No histological diagnosis of this tumour was established.

Case 4 (III 11, Figure 1)

A 15-year-old girl had constipation and soiling from birth. Investigation revealed anorectal stenosis, sacral agenesis, a presacral mass and a separate anterior sacral meningocele. Laparotomy demonstrated a presacral mass 5 cm in diameter adherent to the rectum and a bicornuate uterus. The mass was excised and the patient made a satisfactory recovery. The histological features were those of a benign cystic teratoma. Later, through a lateral sacral approach, the anterior sacral meningocele was excised with release of a tethered filum terminale. Continuing faecal incontinence led to a sigmoid colostomy.

Associated features in this case included bacterial meningitis and hydrocephalus in infancy, recurrent urinary tract infections, bilateral duplex ureters, hydronephrosis and severe vesicoureteric reflux. Urinary incontinence led ultimately to diversion to an ileal conduit.

Discussion

Although the association between sacral agenesis, anterior sacral meningocele and anorectal malformation was recognized by Kennedy as early as 1926[3], it was not until 1981 that Currarino *et al.* recognized these disorders as a syndrome complex explained by a common embryogenesis. The three main features are an anterior sacral defect, congenital anorectal stenosis or another type of low anorectal malformation, and a presacral mass. This may be a meningocele, a teratoma, an enteric cyst, or a combination of these. Our kindred demonstrates that in members of the same family the complete syndrome of defects is present in only a minority of cases. Tunell *et al.*[4] found sacral defects in 36 of 106 patients with imperforate anus, but only one of these had an anterior sacral meningocele. Renshaw found anorectal malformation in 11 of 23 cases with sacral defects[5].

Currarino *et al.*[1] proposed that abnormal endoectodermal adhesions and notochordal defects in early fetal life may result in a fistula between the gut and the spinal canal with enteric elements ventrally and neural elements dorsally. This abnormality appears to be a variant of the split notochord syndrome seen elsewhere in the spinal column[6,7]. Partial resorption of the fistula would give rise to an anterior sacral meningocele or a retrorectal enteric cyst. The combination of these enteric and neuroectodermal elements with mesodermal elements from developing somites could explain the formation of a presacral teratoma.

The occurrence of Currarino's triad of anomalies is familial in more than 50 per cent of cases[8] and diagnosis should prompt

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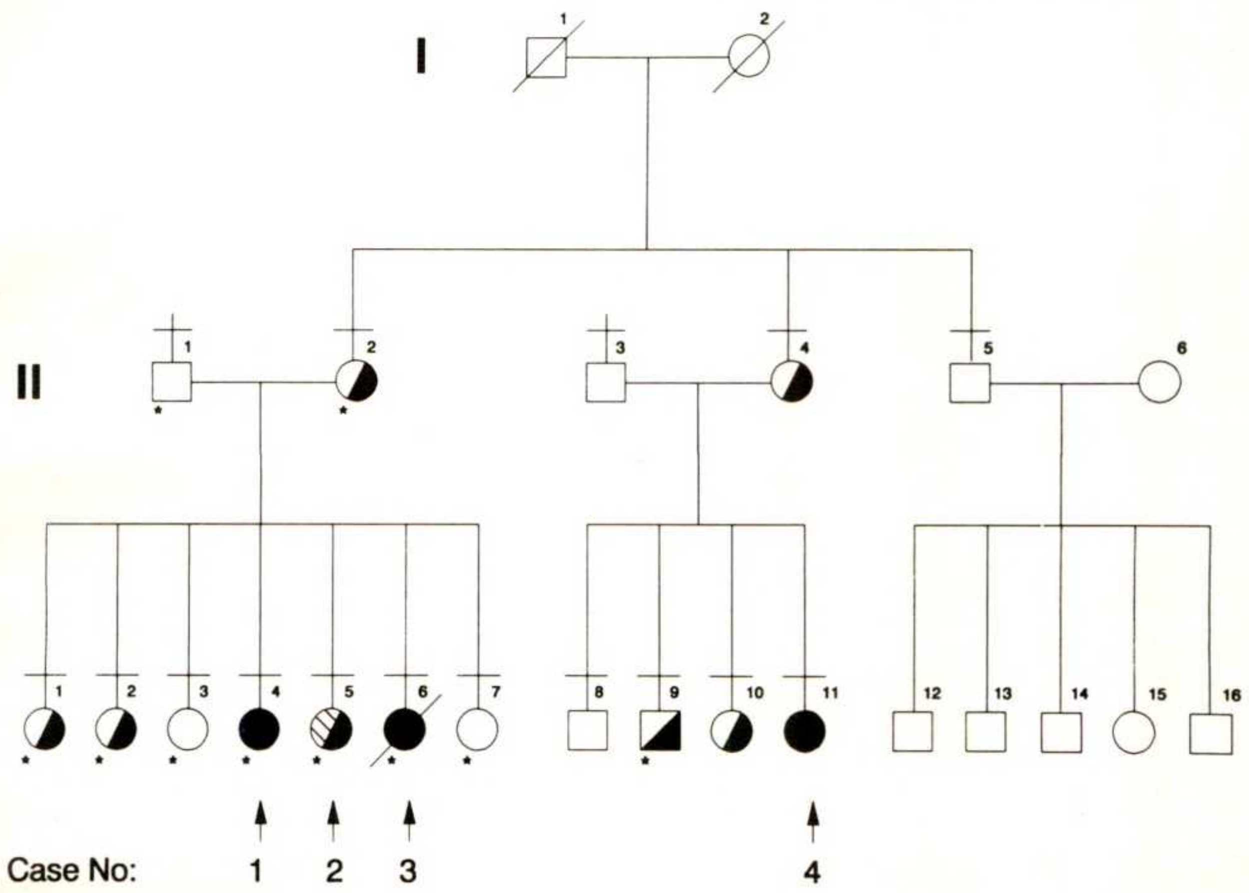

Figure 1 *Family pedigree.* ■, ●, *Sacral agenesis, presacral mass and anorectal stenosis;* ▨, ◍, *sacral agenesis and presacral mass;* ◪, ◑, *sacral agenesis;* □, ○, *evaluated radiologically;* *, *spina bifida occulta*

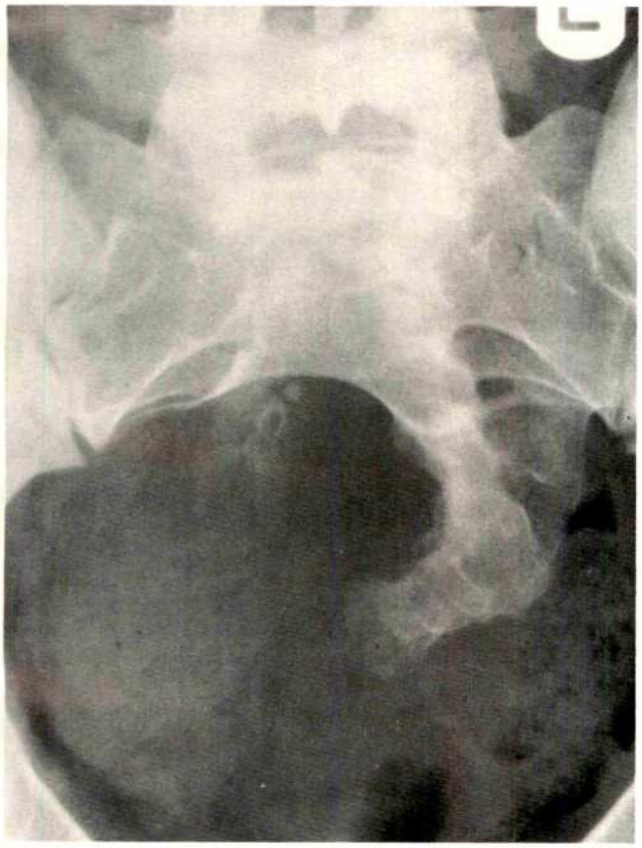

Figure 2 *Plain radiograph of the sacrum in case 2 demonstrating sacral agenesis with absence of the third, fourth and fifth segments on the right side*

evaluation of remaining family members by sacral radiography. Cohn and Bay-Neilson reported that 60 of 69 known patients with anterior sacral meningocele were female and suggested an X-linked dominant pattern of inheritance[9]. Other reports however have suggested autosomal dominant transmission[10,11]. Our own kindred is consistent with the latter mode of inheritance.

Of the 40 reported cases of the complete triad up to 1984, 21 had meningocele alone, 17 had benign teratoma and two had enteric cysts[8]. Of our four cases one had a teratoma alone (case 3) and three had a combination of anterior sacral meningocele and presacral teratoma (cases 1, 2 and 4), bringing to 12 the number of reported cases with this combination[8,11–14]. The association of rectovaginal fistula (case 1), bicornuate or subseptate uterus (cases 1, 2 and 4), or hereditary spherocytosis (case 1) with the Currarino triad have not been described, although one of Currarino *et al.*'s patients had a septate vagina[1]. Other associated anomalies in our patients are well described including hydronephrosis, vesicoureteric reflux, urinary incontinence and tethering of the cord with secondary hydrocephalus[11,15].

The relationship between spina bifida occulta and sacral agenesis has not previously been considered although Kenefick reported this abnormality in two patients with sacral agenesis[16]. Ten patients in the present kindred have spina bifida occulta, seven of whom have sacral agenesis. While it appears likely that spina bifida occulta is associated with sacral agenesis, its coincidental occurrence in one father (II 1, *Figure 1*) obscures its inheritance and its relationship to sacral agenesis.

The presentation of the Currarino triad varies with the degree of anorectal and presacral abnormality. The majority present in infancy with intractable constipation but presentation with urinary tract infections, low back pain, headache, recurrent meningitis and dystocia have all been recorded[12].

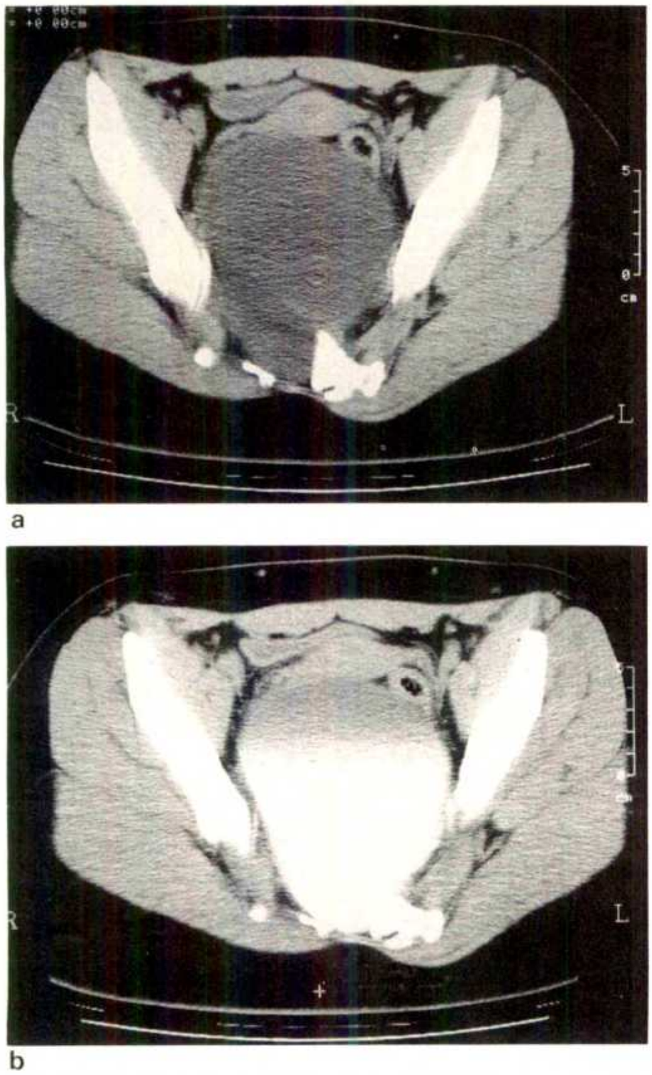

Figure 3 **a** *Control computed tomographic scan of the pelvis demonstrating a large presacral mass and right-sided sacral agenesis in case 2. The rectum, uterus and bladder are displaced anteriorly.* **b** *Computed tomographic myelogram demonstrating a large anterior sacral meningocele filling with contrast in case 2*

Recurrent perianal sepsis (case 1) suggests a presacral teratoma. The finding of sacral agenesis should lead one to suspect a presacral mass and, if supported by clinical examination, computed tomographic myelography should be performed[8,17,18]. The insidious development of a presacral mass (cases 1 and 2) emphasizes the importance of prolonged follow-up of all patients with sacral agenesis. The importance of recognizing the triad lies in the high morbidity and mortality rates associated with the presacral lesion. Recurrent meningitis, obstetric and urinary tract complications lead to a mortality rate of 30 per cent in cases managed without surgery[19]. Rarely, malignant change may occur in a presacral teratoma[17,20].

Surgical excision, following detailed radiological evaluation, is the treatment of choice for a presacral mass. The popular approach to anterior sacral meningocele is retroperitoneal using the Kraske parasacral technique or a sacral laminectomy[12,17]. Identification and ligation of the neck of a meningocele is important[12]. The transabdominal approach, the approach of choice to a presacral teratoma, is said to be associated with technical difficulty and a high incidence of meningitis in the presence of a meningocele[12]. We experienced no difficulty in obtaining adequate exposure to ligate the neck of the meningocele transabdominally in case 2.

This kindred demonstrates autosomal dominant inheritance of sacral agenesis and also its relationship to the other features of the Currarino triad. Greater awareness of this syndrome will lead to improved diagnosis. Insidious development of a presacral mass may occur in a patient with sacral agenesis, making prolonged follow-up essential. A careful search for a presacral lesion in these patients, with surgical excision when present, is advised to prevent future morbidity and mortality.

References

1. Currarino G, Coln D, Votteler T. Triad of anorectal, sacral, and presacral anomalies. *Am J Radiol* 1981; **137**: 395–8.
2. Puri P, O'Donnell B. Familial sacral anomalies. *Z Kinderchir* 1975; **17**: 389–92.
3. Kennedy RLJ. An unusual rectal polyp: anterior sacral meningocoele. *Surg Gynecol Obstet* 1926; **43**: 803–4.
4. Tunell WP, Austin JC, Barnes PD, Reynolds A. Neuroradiological evaluation of sacral abnormalities in imperforate anus complex. *J Pediatr Surg* 1987; **22**: 58–61.
5. Renshaw TS. Sacral agenesis. *J Bone Joint Surg* 1978; **60**: 373–83.
6. Kirwan WO, Walbaum PR, McCormack RJ. Cystic intrathoracic derivatives of the foregut and their complications. *Thorax* 1973; **28**: 424–8.
7. Bentley JFR, Smith JR. Developmental posterior enteric remnants and spinal malformations. *Arch Dis Child* 1960; **35**: 76–86.
8. Kirks DR, Merten DF, Filsto HC, Oakes WJ. The Currarino triad: complex of anorectal malformation, sacral bony abnormality and presacral mass. *Pediatr Radiol* 1984; **14**: 220–5.
9. Cohn J, Bay-Neilson E. Hereditary defect of the sacrum and coccyx with anterior sacral meningocoele. *Acta Pediatr Scand* 1969; **58**: 268–74.
10. Ashcraft KW, Holder TM. Hereditary presacral teratoma. *J Pediatr Surg* 1974; **9**: 691–7.
11. Yates VD, Wilroy RS, Whitington GL, Simmons JCH. Anterior sacral defects: an autosomal dominantly inherited condition. *J Pediatr* 1983; **102**: 239–42.
12. Oren M, Lorber B, Lee SH, Truex RC, Gennaro AR. Anterior sacral meningocoele: report of five cases and review of the literature. *Dis Colon Rectum* 1977; **20**: 492–505.
13. Werner JL, Taybi H. Presacral masses in childhood. *AJR* 1970; **109**: 403–10.
14. Heij HA, Moorman-Voestermans CG, Vos A, Kneepkens CM. Triad of anorectal stenosis, sacral anomaly and presacral mass: a remediable cause of severe constipation. *Br J Surg* 1990; **77**: 102–4.
15. Holthusen W, Birtel T, Brinkmann B, Gunkel J, Janneck C, Richter E. The Currarino triad: an autosomal dominant inherited complex anorectal malformation, sacrococcygeal defect and presacral tumor. Observation of 9 further cases. *ROFO* 1985; **143**: 83–9.
16. Kenefick JS. Hereditary sacral agenesis associated with presacral tumours. *Br J Surg* 1973; **60**: 271–4.
17. Jao SW, Beart RW, Spencer RJ, Reiman HM, Ilstrup DM. Retrorectal tumours. *Dis Colon Rectum* 1985; **28**: 644–52.
18. Felson B, Spitz HB. Pelvic mass in a 12 year old girl. *JAMA* 1977; **237**: 1255–6.
19. Skinner DW, Jacobson I. Anterior sacral meningocoeles. *J R Coll Surg Edinb* 1983; **28**: 229–32.
20. Hunt PT, Davidson KC, Ashcraft KW, Holder TM. Radiography of hereditary presacral teratoma. *Radiology* 1977; **122**: 187–91.

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Insights gained from the management of problematical anal fistulae at St. Mark's Hospital, 1984–88

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Twenty-four (3·6 per cent) patients with problematical anal fistulae out of 671 with anal fistulae were analysed to assess the reasons for their recurrences and ultimate outcome. Thirteen patients (group A) had recurrent fistulae despite two definitive attempts at surgery at this hospital (median number of previous procedures before referral to this hospital was two, range 0–7; median number of definitive procedures at this hospital was three, range 3–4). In five of these patients, the reason for recurrence was missed primary (four cases) or secondary tracks (one case) at earlier operations. Five patients required multiple operations related to the use of setons. Eleven other patients (group B) required colostomy construction, eight because of severe perianal sepsis, two because of complex fistulae, and one for postrectal dermoid. Fistula healing occurred ultimately in all patients in group A afer a median of 14 months (range 4–38 months). In group B, fistula healing occurred in eight patients after a median of 7·5 months (range 2–55 months) after colostomy construction. Only one patient has had a proctectomy, and five still have their colostomy. Of the other 18 patients, continence is normal in 14, there is mucus leakage in two, flatus incontinence in one and faecal incontinence in one. In conclusion, persistent attempts to resolve anal fistulae in difficult cases are frequently successful in the long term and result in good continence.

The majority of anal fistulae are simple and pose few problems[1,2]. Fistulae are usually considered to be more difficult to treat when the primary track crosses the upper part of the external sphincter or when the track is suprasphincteric or extrasphincteric. In these circumstances various strategies have been developed, such as the use of loose or tight setons or advancement flaps, to preserve continence as much as possible[3–5]. Another sort of difficult fistula is one that continually recurs despite repeated skilled attention. Overlooked additional internal openings or further secondary tracks may be responsible for some of these recurrences, but when repeated attempts to heal one of these intransigent fistulae have failed, the surgeon and the patient not unnaturally may become somewhat demoralized.

We have identified a group of patients without an underlying predisposing cause such as inflammatory bowel disease, tuberculosis or cancer, whose fistulae have been very difficult to heal. In those whose fistulae were eventually healed, we have tried to highlight the sequence of events that led ultimately to healing. In those for whom fistula surgery was ultimately unsuccessful, we have attempted to establish the reasons.

Patients and methods

Fistulae are classified according to Parks' classification[6], and for the purpose of this paper a problematical fistula is defined as a fistula that recurred despite two previous definitive attempts at treatment at this hospital (group A had such problematical fistulae), or a fistula that required a colostomy for its management (group B).

The operating theatre and hospital record books for 1984–88 inclusive were reviewed. All patients who fitted the above definitions were included in the study. All patients with Crohn's disease, tuberculosis or cancer were excluded.

Results

During the study period, a total of 671 patients with anal fistulae were operated on in this hospital.

Group A

There were 13 (1·9 per cent) patients in whom the fistula remained unhealed despite two definitive operations at this hospital. Eleven were men and two were women. The median age was 51 years (range 31–75 years). None had any other associated diseases. The median duration of anal symptoms before the first operation at this hospital was 18 months (range from 1 week to 156 months). The median number of previous procedures before referral to this hospital was two (range 0–7). The median number of definitive procedures at this hospital was three (range 3–4). Median time, from the first operation at this hospital to healing, was 14 months (range 4–38 months).

The reasons for initial failure were: wrongly diagnosed primary tracks or missed secondary tracks (five cases), multiple procedures related to the use of setons (five cases), and repeated bridging of the wound or wound revision (three cases). This means that of the 13, five could be considered inadvertent failures whereas the other eight had an ultimately successful although prolonged plan of therapy. *Figure 1* shows details of the five missed or wrongly diagnosed tracks.

All patients in group A ultimately ended up with a successfully healed fistula. The final procedures that led to fistula healing were as follows: (a) seven patients required laying open of a remnant intersphincteric or superficial track, five of which followed seton usage. One patient with a seton and a remnant intersphincteric track also required drainage of a supralevator extension; (b) five patients required laying open

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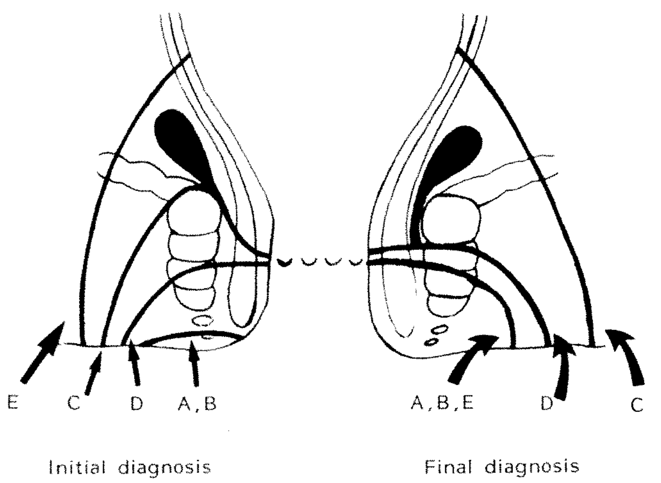

Figure 1 *Diagram showing the tracks that were wrongly diagnosed or missed. Patients A and B were initially considered to have superficial tracks but were ultimately found to have high trans-sphincteric tracks. Patient C was considered to have a suprasphincteric track with a supralevator abscess; this was subsequently recognized as an extrasphincteric track. Patient D had a trans-sphincteric track, but a supralevator extension was overlooked. Patient E was initially thought to have an extrasphincteric track, but this was later confirmed to be a trans-sphincteric track*

of a remnant transsphincteric track by division of part of the external anal sphincter. Two of these followed seton usage and three did not; (c) in the final patient, a missed extrasphincteric track was found after initial treatment with a seton failed to heal a wrongly diagnosed fistula.

Ten patients have normal continence, two have only mucus leakage, and one has incontinence of flatus alone.

Group B

Eleven (1·6 per cent) patients required a proximal defunctioning colostomy, two of whom were referred after colostomy construction elsewhere. There were ten men and one woman. The median age was 46 years (range 31–63 years). One patient had hepatic cirrhosis with myelodysplasia and another had significant depression. The other nine patients did not have any significant illness. The median duration of symptoms before the first operation at this hospital was 18 months (range 1–192 months). The median number of previous operations before referral to this hospital was two (range 0–8). The median number of definitive operations required in this hospital was four (range 1–7), which included colostomy construction, colostomy closure and sphincter repair. The median time required for healing from the time of construction of the colostomy was 7·5 months (range 2–55 months). One fistula remained unhealed 18 months after colostomy construction. *Table 1* show the various types of track in the patients managed with a defunctioning colostomy.

Eight patients required their colostomy for severe anal sepsis. Two others had a stoma made because of a recto-suprapubic fistula and an extrasphincteric track respectively, and one paient had a colostomy constructed at the same time as excision of a presacral dermoid.

Eight patients went on to complete healing of the anal fistulae. The median time required to achieve healing after colostomy construction was 7·5 months (range 2–55 months). One patient remains unhealed at 18 months, and a missed extrasphincteric track was recently found in this patient.

Six patients have had their colostomies closed. Four regained normal anal continence. One patient suffers major faecal leakage despite two attempts at repairing his anal sphincter, but continues without a colostomy and is managed with constipating drugs. One patient required reconstruction of the colostomy following recurrent anal sepsis after initial colostomy closure and must be considered still to have an active fistula.

Five patients continue to have colostomies. Two could not retain porridge enemas and are candidates for sphincter repair. One other patient has had a recent sphincter repair and now awaits colostomy closure. Two more patients remain unhealed after colostomy construction. One required a proctectomy and the other, in whom a missed track was recently discovered, remains unhealed 18 months after colostomy construction.

Discussion

Problematical fistulae are, by definition, difficult to treat and may be followed by a high rate of recurrence or by anal incontinence[1]. We have identified a few pitfalls which have led to some fistulae becoming problematical. The many attempts to resolve these intransigent anal fistulae have on the whole been successful and have given good functional results. The reasons for the various difficulties are varied but fall broadly into the following categories: mistaken assessment of the primary track, overlooking of a secondary track, attempts to preserve anal continence where the primary track crosses the external sphincter at a high level, and severe perineal sepsis.

The primary track can usually be inferred by identifying the internal and external openings and by feeling between the two points with a well lubricated finger. Fistulography has not been very useful[7]. Methylene blue can be used to show whether an internal opening exists but the tissues tend to become very stained once the track has been cut into. Another aid to clinical examination is the injection of hydrogen peroxide into the external opening and the observation of a stream of bubbles from the internal opening[8]. In practice, however, such manoeuvres are rarely necessary.

Endoanal ultrasonography has not been as useful as was hoped in the correct identification of complex fistulae[9], because of an inability to see both tracks which lie outside the sphincter complex and tracks that lie above the anal canal. Indeed digital examination has been shown to be superior to anal endosonography at this hospital[10]. The surgeon is alerted to the possibility of a supralevator extension by feeling induration in front of the coccyx/sacrum. This can be quite difficult to detect because the induration may be so firm as to feel like bone itself and so be ignored. Comparison of the right with the left side may be helpful in distinguishing any abnormality.

Probing areas of persistent granulation tissue after curettage of the laid-open track is probably the most helpful way of detecting secondary tracks at operation. But if overlooked, examination under anaesthesia of the wound some 2–3 weeks later will show a bead of pus and granulation tissue that will not curette away.

There are various ways of attempting to preserve continence with fistulae that cross the external sphincter at a high level, such as the use of loose setons, advancement flaps or coring out the track and primary suture[11]. All of them run a higher risk of

Table 1 *Types of primary and secondary tracks in patients managed with a defunctioning colostomy*

Primary tracks	Secondary tracks/abscesses	*n*
Intersphincteric	Supralevator and/or infralevator	2
Trans-sphincteric	Supralevator	3
Trans-sphincteric	Rectosuprapubic	1
Suprasphincteric	Supralevator and infralevator	2
Extrasphincteric	Nil	1
Extrasphincteric	Supralevator	1
Extrasphincteric	Presacral and postsacral	1

failure than simple laying open or the use of a tight seton, but either of these last two can always be used should they fail. A loose seton can be especially useful when an inexperienced surgeon is confronted by a difficult fistula; approximately 44 per cent will heal after seton removal without external anal sphincter division[3].

The use of a colostomy is usually precipitated either by the need to lay open so much muscle that incontinence will result or because of the sudden development of severe perineal sepsis. In the first case, the object is to get the fistula to heal and then perform a delayed sphincter repair. Sphincter repairs were performed on three patients in this series and another two patients who still have colostomies are candidates for sphincter repair. Of the six patients whose colostomies have been closed, four have normal continence.

There has been research into the microbial flora of acute perianal and ischiorectal abscesses but we are unaware of any studies on the microbiology of chronic anal fistulae. The occurrence of severe perineal sepsis in some of our cases that necessitated the urgent construction of a colostomy could simply have been caused by faecal contamination of the wound. Minor perineal pain and fever after fistula surgery, or indeed following review of the fistula wound under anaesthesia, is not uncommon. It suggests that prophylactic antibiotics might be used in some cases which, except in diabetic patients, has not been the past practice at this hospital.

In conclusion, most problematical fistulae can be healed and few patients will end up with a permanent stoma. These results hold out hope for both patient and surgeon alike as persistent attempts are often rewarded in patients with recurrent fistulae.

References

1. Abcarian H, Dodi G, Gironi J *et al.* Symposium. Fistula-in-ano. *Int J Colorect Dis* 1987; **2**: 51–72.
2. Shouler PJ, Grimley RP, Keighley MRB, Alexander-Williams J. Fistula-in-ano is usually easy to manage surgically. *Int J Colorect Dis* 1986; **1**: 113–15.
3. Thomson JPS, Ross AHM. Can the external anal sphincter be preserved in the treatment of transphincteric fistula-in-ano. *Int J Colorect Dis* 1989; **4**: 247–50.
4. Held D, Khubchanani I, Sheets J, Stasik J, Rosen L, Riether R. Management of anorectal horseshoe abscess and fistula. *Dis Colon Rectum* 1986; **29**: 793–7.
5. Christensen A, Nilas L, Christiansen J. Treatment of trans-sphincteric anal fistulas by the seton technique. *Dis Colon Rectum* 1986; **29**: 454–5.
6. Parks AG, Gordon PH, Hardcastle JD. A classification of fistula-in-ano. *Br J Surg* 1976; **63**: 1–12.
7. Kuijpers HC, Schulpen T. Fistulography for fistula-in-ano. *Dis Colon Rectum* 1985; **28**: 103–4.
8. Glen DL. Use of hydrogen peroxide to identify internal opening of anal fistula and perianal abscess. *Aust NZ J Surg* 1986; **56**: 433–5.
9. Law PJ, Talbot RW, Bartram CI, Northover JMA. Anal endosonography in the evaluation of perianal sepsis and fistula-in-ano. *Br J Surg* 1989; **76**: 752–5.
10. Seow-Choen, Burnett S, Bartram CI, Nicholls RJ. A comparison between anal endosonography and digital examination in the evaluation of anal fistulae. *Br J Surg* 1991; **78**: 445–7.
11. Phillips RKS. Management of fistula-in-ano. *Curr Med Lit Gastroenterol* 1989; **8**: 71–5.

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Colon perforation during colonoscopy: surgical *versus* conservative management

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A survey of endoscopy units in the West Midlands, UK, was undertaken to ascertain the management of colonic perforation during colonoscopy. Fifteen perforations were reported from a total of 17 500 colonoscopies performed in 14 units (a rate of 0·09 per cent). In seven patients the diagnosis was suspected or diagnosed immediately and in the remaining eight 2–72 h later. Four patients with associated pathology (carcinoma, Crohn's disease, ulcerative colitis and a polyp) had resection and primary anastomosis. Seven patients had a simple oversew, four of these having had a delayed diagnosis. In four cases the site of perforation was not identified, but only one patient had conservative treatment. Three patients had drainage and a defunctioning colostomy. There was no significant morbidity following treatment. It is recommended that patients who have had a good bowel preparation should be treated conservatively unless there is a large perforation or an underlying carcinoma.

Colonoscopy is widely used in the diagnosis and treatment of colonic disease. Colonic perforation remains an important complication and the reported incidence varies from 0·1 per cent to 0·8 per cent[1–15]. The incidence of perforation seems to be higher following therapeutic procedures (0·2–0·5 per cent) than after diagnostic colonoscopy (0·1–0·3 per cent)[5,11–15]. Reported mortality rates from this complication are variable: in the St. Mark's series there were no deaths in six patients[9] but in the large survey by Smith[12] from North America there were two (3 per cent) deaths in 72 patients. In other series containing five or more patients, a mortality rate of up to 50 per cent has been reported[1,2,4,5,7,9,11–16]. Collectively there have been 27 (10·8 per cent) reported deaths in 251 patients with colonoscopic perforations[1,2,4,5,7,9,11–16].

Successful management of colonoscopic perforation by conservative treatment has been reported[3,12,14,17–19] but management remains controversial. Carpio *et al.*[2] suggested surgery if the perforation is recognized immediately, and Friedrichs[4] and Potvliege *et al.*[20] recommended surgery in all instances. Some recommend conservative management only if there are radiological signs of a retroperitoneal perforation[18,21]. With some exceptions[1,2,4,9,13,16,20] previous series have failed to give precise findings at laparotomy and details of the operations undertaken, making it difficult to reach objective conclusions.

A survey of the management of colonoscopic perforation was therefore undertaken in the West Midlands Regional Health Authority with particular emphasis on operative findings and procedures.

Patients and methods

Seventeen endoscopy units in the West Midlands Regional Health Authority, UK, were sent a postal questionnaire requesting information on colonoscopic perforation. The questionnaire was designed in two parts. The first part requested general information concerning the overall practice of the endoscopy unit. The second part requested information specific to each individual patient, recording underlying pathology and treatment and any determinable risk factors associated with the perforation. Particular information was requested regarding the site of perforation, if this could be located, and the precise operation undertaken.

Results

Fourteen of the 17 units replied. The data supplied were based on computer records in two units and by endoscopy record manual searches in the remainder. Memory recall had to be relied upon for diagnosis in patients with a delayed perforation because this information was not usually recorded on the endoscopy chart. A total of 17 500 colonoscopies had been performed over a median of 6 years (range 4–15 years). Fifteen perforations from six units were reported (*Table 1*). Seven of the perforations occurred during therapeutic procedures and eight during diagnostic examination. The data did not accurately reveal how many of the colonoscopies were therapeutic and how many were diagnostic.

Twelve of the 15 perforations occurred in the hands of colonoscopists who had performed over 150 colonoscopies at the time of perforation, and all except one perforation was produced by a consultant. The majority of colonoscopies were performed by consultants and in only seven of the units were colonoscopies routinely performed by junior staff in training. Only one perforation occurred during an examination under

Table 1 *Details of perforations and procedures used in each of the 14 units*

Endoscopy unit	No. of endoscopists	No. of procedures	No. of perforations
A	3*	420	2†
B	2	1200	6
C	2*	2000	–
D	2*	1800	2
E	2	1600	–
F	2	1900	3
G	1	1000	–
H	1	1500	–
I	3*	480	1
J	4*	400	1
K	3	1400	–
L	4*	1200	–
M	3	1000	–
N	4*	1600	–

* Unit that trains junior staff; † one perforation occurred under general anaesthesia

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Table 2 *Clinical details of patients with colonic perforation occurring during diagnostic procedures*

Age (years)	Sex	Reason for examination	Site of perforation	Time of diagnosis	Treatment
24	F	Crohn's disease	Sigmoid colon	Immediate	Resection and anastomosis
38	M	Ulcerative colitis	Sigmoid colon	Immediate	Resection and anastomosis
73	M	Carcinoma	Sigmoid colon	Immediate	Resection and anastomosis
75	F	Diverticulosis	Sigmoid colon	Immediate	Oversew
72	F	Diverticulosis	Sigmoid colon	Immediate	Oversew
46	M	Surveillance	Sigmoid colon	Immediae	Oversew
73	F	Anaemia	Unidentified	Immediate	Drainage and defunctioning colostomy
63	F	Diverticulosis	Unidentified	2 h	Drainage and defunctioning colostomy

Table 3 *Clinical details of patients with colonic perforation occurring during therapeutic procedures*

Age (years)	Sex	Reasons for examination	Site of perforation	Time of diagnosis (h)	Treatment
48	F	Polyps (transverse colon and sigmoid colon)	Unidentified	2	Conservative
58	F	Polyp (sigmoid colon)	Caecum	4	Resection, oversew and colostomy
62	M	Polyp (sigmoid colon)	At polyp	4	Oversew
71	F	Polyp (sigmoid colon)	At polyp	24	Oversew
74	M	Polyp (sigmoid colon)	At polyp	24	Oversew
58	M	Polyp (ascending colon)	At polyp	30	Oversew
66	M	Polyp (sigmoid colon)	Unidentified	72	Drainage and defunctioning colostomy

general anaesthesia. The incidence of perforations was six out of 7900 (0·08 per cent) procedures in units training junior staff compared with nine out of 9600 (0·09 per cent) in the remainder. Perforations in patients receiving intravenous sedation occurred in 13 out of 14 280 (0·09 per cent) procedures compared with one out of 3220 (0·03 per cent) in units in which this was never or only occasionally used.

The colonoscopist considered the procedure to be difficult in seven of the eight diagnostic perforations but difficult in only one of the seven therapeutic perforations. In no case was inadequate bowel preparation thought to contribute to the perforation.

Clinical details of the site of perforation, time of diagnosis of perforation with respect to the time of colonoscopy, underlying pathology and subsequent management are given in *Tables 2* and *3*. There were eight women and seven men who sustained perforations, with a median age of 63 years (range 24–75 years). Seven (47 per cent) patients had a simple oversew and four (27 per cent) had resection. Three (20 per cent) patients had drainage with a defunctioning colostomy because the site of perforation could not be identified. The colostomy was closed uneventfully within 6 weeks in each patient. Perforation was confirmed at laparotomy by the finding of pneumoperitoneum except in one patient who was treated conservatively with nasogastric suction and intravenous antibiotics. Endoscopic excision of a polyp from the transverse colon was performed 3 months later by the same colonoscopist without difficulty.

None of the patients sustained major complications and there were no deaths. In none of the patients undergoing surgery was poor bowel preparation given as an indication for surgery; indeed, this was described as good ($n=7$) or excellent ($n=8$).

Discussion

Colonoscopic perforation may be due to direct perforation with the instrument tip, antimesenteric tears secondary to looping of the instrument, pneumatic perforation due to excessive air insufflation, or it may be caused by biopsy, diathermy or polypectomy. We reported a combined diagnostic and therapeutic perforation rate of 0·09 per cent, which is low. Crespon *et al.*[3] in 1975, however, reported only one perforation in 1000 colonoscopies. It is noteworthy that previous large series have also relied on surveys similar to that in the present study, and combined perforation rates varied from 0·22 to 0·36 per cent[5,11,12].

The site of perforation was identified in only 11 of the 15 patients. There was one pneumatic perforation of the caecum following a difficult polypectomy of a lesion in the sigmoid area and in the sigmoid colon in nine of the other cases. As in other series, the sigmoid colon is the site at greatest risk because it is a difficult area to negotiate and is the commonest site for polypectomy[1,2,4,5,9].

Seven of the eight diagnostic perforations were detected or suspected during the procedure and five of these seven examinations were considered technically difficult. The majority of the perforations occurring during therapeutic colonoscopy, however, were not detected until 24–72 h later and only one of these procedures was considered difficult at the time of the colonoscopy. Some of these perforations may have occurred as a result of full-thickness diathermy injury resulting in delayed perforation at the damaged site.

Although one perforation occurred under general anaesthesia, this does not appear to be a major risk factor in experienced hands[6] despite previous anecdotal evidence[11–13]. In the present study, the incidence of perforation was nearly threefold in units using analgesia routinely, but with only 15 perforations in the whole series no statistically significant conclusion can be reached.

Failure to localize the site of perforation at laparotomy has been previously described but not commented on[1,4]. These patients may have been managed conservatively since failure to complete the colonoscopy or perform a polypectomy is not an added indication for laparotomy. This may be completed at a later stage as indicated in one patient.

Table 4 *Mortality rate in relation to type of treatment in patients undergoing colonoscopy where series contained five or more cases of perforation*

Series	Year	Colonoscopies	Treatment of perforation			Mortality rate (%)
			Surgery	Conservative	Total	
Rogers *et al.*[11]	1975	31 512	16 (2+)	1	17 (2+)	12
Geenen *et al.*[7]	1975	1 106	8	0	9 (1+)*	11
Smith[12]	1976	20 139	47 (2+)	25	72 (2+)	3
Frumorgen and Demling[5]	1979	35 892	–	–	78 (10+)	13
Höllerl *et al.*[16]	1980	622	5	0	5	0
Freidrichs[4]	1983	3 800	8 (4+)	0	8 (4+)	50
Macrae *et al.*[9]	1983	5 000	6	1 (†)	6	0
Vincent and Smith[13]	1983	1 547	6	0	6	0
Dubas and Rohner[14]	1985	5 550	13 (3+)	4	18 (4+)‡	22
Brynitz *et al.*[1]	1986	1 748	11 (1+)	0	11 (1+)	9
Riertsen *et al.*[15]	1987	4 593	5	2	7	0
Caripo *et al.*[2]	1989	5 424	9 (3+)	5	14 (3+)	21
Present series	1991	17 500	14	1	15	0
Total		134 383	148 (15+)	39 (1+)	266 (27+)	
Mortality rate (%)		0·02	10·1	3	10·2	

(+), Number of deaths; * perforation unrecognized and found at post mortem only; † failed conservative treatment followed by surgery; ‡ one patient moribund and not operated on

The infrequent use of conservative management of perforations is partly due to the sparsity of information regarding colonoscopic complications in the surgical literature and because an average district general hospital is unlikely to experience more than one case a year. A survey of published series shows a mortality rate for surgical treatment which is greater than that for conservative treatment (*Table 4*). As reported by Adair and Hishon[19] and Andresen[22], the authors have personal experience with four patients sustaining perforation following rigid sigmoidoscopic polypectomy managed conservatively with equal success. A trial of conservative therapy would therefore seem to warrant more frequent consideration. On the other hand, delaying surgery in some situations may lead to an irretrievable situation[14]. It is thus important for endoscopists to discuss this clinical situation with the surgeon at an early stage.

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References

1. Brynitz S, Kjaergard H, Struckmann J. Perforations from colonoscopy during diagnosis and treatment of polyps. *Ann Chir Gynaecol* 1986; **75**: 142–5.
2. Carpio G, Albu E, Gumbs MA, Gerst PH. Management of colonic perforation after colonoscopy. *Dis Colon Rectum* 1989; **32**: 624–6.
3. Crespon B, Housset P, Mendez J, Berman H, Debray C. Bilan de 1000 colocopies. *Arch Fr Mal Appl Dig* 1975; **64**: 299–308.
4. Friedrichs D. Diagnose und therapie der endoskopischen dickdermperforation. *Medizionische Welt* 1983; **34**: 75–6.
5. Fruhmorgen P, Demling L. Complications of diagnostic and therapeutic colonoscopy in the Federal Republic of Germany. Results of an enquiry. *Endoscopy* 1979; **2**: 146–50.
6. Kjaergard H, Nordkild P, Geerdsen, Dyrberg V. Anaesthesia for colonoscopy. An examination of the anaesthesia as an element of risk at colonoscopy. *Acta Anaesthesiol Scand* 1986; **30**: 60–3.
7. Geenen JE, Schmidt MG, Wu WC, Hogan WJ. Major complications of colonoscopy: bleeding and perforation. *Ann J Dig Dis* 1975; **20**: 231–5.
8. Konberg D, Hage E, Adamsen S, Deichgraber E. Follow-up after colorectal polypectomy. I. A comparison of the effectiveness of repeated examinations of the colon every 6 and 24 months after removal of stalked polyps. *Scand J Gastroenterol* 1983; **18**: 1089–93.
9. Macrae FA, Tan KG, Williams CB. Towards safer colonoscopy: a report on the complications of 5000 diagnostic or therapeutic colonoscopies. *Gut* 1983; **24**: 376–83.
10. Nelson RL, Abcarian H, Prasad ML. Iatrogenic perforation of the colon and rectum. *Dis Colon Rectum* 1982; **25**: 305–8.
11. Rogers BHG, Silvis SE, Nebel DT, Sugawa C, Mandelstram P. Complications of flexible fibreoptic colonoscopy and polypectomy. *Gastrointest Endosc* 1975; **22**: 73–7.
12. Smith LE. Fibreoptic colonoscopy: complications of colonoscopy and polypectomy. *Dis Colon Rectum* 1976; **19**: 407–12.
13. Vincent M, Smith LE. Management of perforation due to colonoscopy. *Dis Colon Rectum* 1983; **26**: 61–3.
14. Dubas F, Rohner A. Perforations colo-rectalses iatrogenes. *Helv Chir Acta* 1985; **52**: 681–6.
15. Reiertsen O, Skjoto J, Jaconsen CD, Rosseland AR. Complications of fibreoptic gastrointestinal endoscopy – five years experience in a central hospital. *Endoscopy* 1987; **19**: 1–6.
16. Höllerl G, Stenzl, Stadler H. Prophylaxe und therapie der dickdarmperforation bei der diagnostischen fiberkoloscopie. *Z Gastroenterologie* 1980; **18**: 376–809.
17. Wolff WI, Shinya H. A new approach to colonic polyps. *Ann Surg* 1973; **178**: 367–76.
18. Meyers MLA, Ghahremani GG. Complications of fibreoptic endoscopy. *Radiology* 1975; **155**: 301–7.
19. Adair HM, Hishon S. The management of colonoscopic and sigmoidoscopic perforation of the large bowel. *Br J Surg* 1981; **68**: 415–16.
20. Potvliege M, Azagra JS, Clerckx L. Considerations sur les perforations diverticulaires et instrumentales du colon. *Acta Chir Belg* 1984; **84**: 109–12.
21. Verduron A, Delohier JC, Thomsen C, Picker M, Soule JC. Perforation retroperitoneale apres resection endoscopique des polypes coliques. *Gastroenterol Clin Biol* 1983; **7**: 831.
22. Andresen AFR. Perforations from proctoscopy. *Gastroenterology* 1947; **9**: 32–43.

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Colonic complications after toxic tribal enemas

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Tribal enemas obtained from traditional healers are used widely in Southern Africa for a variety of indications. Inclusion of injurious substances such as potassium dichromate may cause serious colonic and renal complications. Nine such patients, in seven of whom chromate use was confirmed, presented after a mean delay of 7·3 days. All patients had bloody diarrhoea and vomiting and three underwent major colonic resection, requiring a total of ten procedures. One patient suffered mechanical perforation of the rectum, with subsequent necrotizing fasciitis, necessitating rectal excision. Eight patients had acute renal failure and seven required dialysis. One patient died. At follow-up one patient has chronic renal failure and only three are completely well. Although local medical practitioners are aware of the problem, the challenge of preventing harmful cultural practices remains.

Purgative enemas form an integral part of traditional medicine in Southern Africa[1,2]. The wide spectrum of indications includes psychosis, constipation, headache and gonorrhoea. Although often self-administered, the enema constituents are usually obtained from a traditional healer (*n'anga* or *sangoma*) who is an authoritarian tribal figure and acts as healer, herbalist, historian[3], exorcist[4] and marriage counsellor[5]. The use of tribal enemas is widespread. Members of the Zulu tribe commonly receive up to three enemas a week[1] and Swazi infants 50 enemas per year[6]. Two analyses of enema usage in South African blacks at Baragwanath Hospital, serving a population of approximately two million in Soweto, Johannesburg, reported frequent administration in 36 per cent (1964)[1] and 62·8 per cent (1978)[6] of patients. Both figures may underestimate the frequency of enema usage because of the difficulties in cross-cultural surveys. Oettlé has extrapolated that at least one million enemas are used monthly in Soweto[7]. Increasing urbanization has resulted in the incorporation in the enema solution of injurious substances as purgatives, in particular dichromates. Although the probable incidence of gastrointestinal complications is low[6], we report nine Xhosa patients requiring hospital treatment, four of whom had a serious or fatal outcome.

Patients

Between January 1980 and November 1989, nine patients were admitted following traditional medicine usage (*Table 1*). The history shown in *Table 1* was sometimes obtained only after persistent questioning. All were treated for gastrointestinal symptoms and eight for acute renal failure. Men predominated (M:F, 2:1) and the mean age was 34·1 years (range 22–48 years).

Results

Patient characteristics, treatment details and outcome are listed in *Table 1*. In seven of the nine cases, dichromate use was confirmed by direct analysis for the agent or by finding high serum chromium levels. In two cases the toxic agent was unknown. Although often self-administered, all substances were obtained from *n'angas*. Indications for usage varied (*Table 1*).

All patients presented after considerable delay (mean 7·3 days, range 2–20 days) when renal or gastrointestinal symptoms were marked. Three patients were shocked on admission and one became so later, after massive rectal bleeding. All patients experienced rectal bleeding and vomiting. Four had haematemesis. All conscious patients experienced mild to severe abdominal pain. One patient developed peritonitis following direct mechanical perforation of the rectum. One patient took *n'anga* medication orally as well as rectally and one only orally. The latter died from multiorgan failure, candida septicaemia and massive upper and lower gastrointestinal haemorrhage. Three patients required emergency surgery. One patient had a defunctioning transverse loop colostomy with subsequent left-sided resection and coloanal anastomosis, another required urgent total colectomy and ileostomy for bleeding, and a third patient had rectal excision and extensive perineal and pelvic debridement for necrotizing fasciitis. A total of ten operations was performed.

Eight patients had acute renal failure, seven of whom required dialysis for a mean of 11·7 days (range 7–26 days). Five of seven survivors who had renal failure on admission now have normal kidney function, one patient was lost to follow-up while the serum creatinine level was still three times normal, and another has mild renal impairment at 24 months. One patient presented in coma with hepatic and renal failure but eventually survived.

Discussion

The colonic and renal complications following tribal enemas, although severe, are uncommon given the predicted frequency of enema administration in the South African black population. In the rural environment, ingredients include herbs, bark, roots, leaves and bulbs[3], and are often administered through a truncated cow's horn or hollow reed. Local plant substances from the superorder Liliiflorae are not always innocuous. Both human and animal deaths attributable to the haemolytic saponins, colchicine-like alkaloids and cardiac glucosides they contain have been documented[8]. With increasing urbanization more effective and readily available purgatives have been substituted and are given with a syringe and rubber tubing. These domestic and industrial agents include thinners, turpentine, chloroxylenol antiseptic (Dettol), ginger, pepper, soap, vinegar, caustics, copper sulphate and potassium permanganate[6,9]. This last is referred to in Xhosa as *zifozonke* or 'cure for all ills' (Professor E. L. Mazwai, personal communication).

Potassium dichromate was implicated in seven of our cases and is widely available for commercial use in electroplating, tanning, cement manufacture and photographic processing[10]. Hexavalent chromium, unlike the inert metallic form, is highly reactive and has powerful oxidizing properties. Multisystem life-threatening sequelae following rapid tissue binding include gastrointestinal ulceration and haemorrhage. Dialysis

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Table 1 *Toxic tribal enemas: clinical details*

Case	Sex	Age	Traditional medicine	Indication	Delay before presentation (days)	Renal failure (*dialysis)	Abdominal pain	Rectal bleeding	Vomiting (*haematemesis)	Gastrointestinal complications	Surgery (no. operations)	Follow-up (months)	Outcome
1	M	41	Enema (dichromate)	Unclear	3	+*	+	+	+*	Dysphagia		Lost	Unknown
2	M	27	Enema (dichromate)	Back pain	>14	+*	Coma	+	+	Hepatic failure		4	Well
3	M	30	Enema (dichromate)	Headache	7	+*	+	+	+*	—		12	Well
4	F	47	Enema (dichromate)	Constipation	7	+*	+	+	+	—		24	Chronic renal failure
5	M	37	Enema (dichromate)	Regular user	4	+*	+	+	+	—		2	Well
6	M	26	Enema and oral dichromate	Psychosis	4	+*	+	+	+	Perforated rectum, peritonitis, necrotizing fasciitis	Pelvic/perineal debridement, rectal excision (4)	14	Neurogenic bladder, colostomy
7	M	48	Oral dichromate	Gonorrhoea	2	+*	+	+	+*	Multiorgan failure, massive haemorrhage		—	Died (necrotic oesophagus and colon)
8	F	22	Enema (? nature)	Abdominal pain	5	—	+	+	+	Colonic stricture	Defunctioned coloanal anastomosis (3)	32	Continence problems
9	F	29	Enema (? nature)	Psychosis	?20	+	+	+	+*	Colonic ulceration, massive haemorrhage	Total colectomy, ileostomy, ileorectal anastomosis (3)	10	Psychosis, satisfactory bowel function

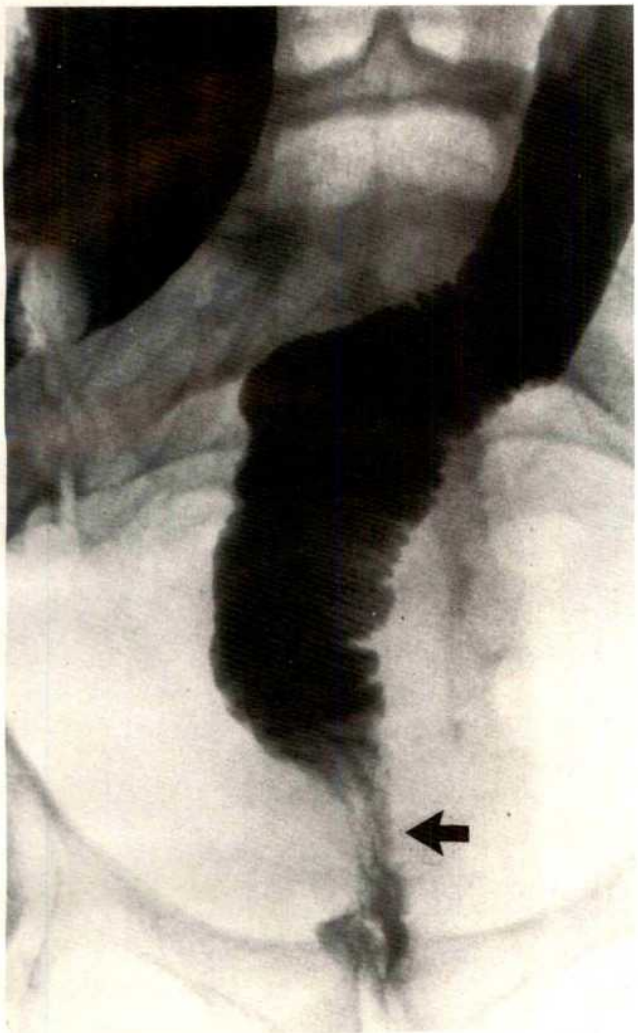

Figure 1 *Barium enema performed 1 month after toxic enema (case 8) showing rectal stricturing (arrow)*

performed after the early period following exposure may not remove dichromate but is supportive.

The early radiological picture of colonic distension and ileus may be gross enough to resemble a toxic megacolon[3]. Similarly, late appearance may be confused with the skip lesions and stricturing of Crohn's disease (*Figure 1*). However, inflammatory bowel disease, although increasing in incidence among black South Africans, is still very rare[11] and generally does not enter the differential diagnosis. An infective cause for the diarrhoea must be excluded and, also, there may be an underlying disorder which caused the patient to seek a healer initially. As in our cases, patients often also experience upper gastrointestinal symptoms, including vomiting and haematemesis, after toxic enema. This is possibly due to a systemic effect, as haematemesis has been described after intravenous chromium injection[12].

Colorectal complications range from a mild reversible superficial inflammatory reaction involving only mucosa and submucosa, to a severe proctocolitis (*Figure 2*) which, with necrosis and full-thickness ulceration, can result in perforation and peritonitis. In case 6, perforation was mechanical and led to the unusual complication of necrotizing fasciitis requiring radical debridement of perineum and pelvis with rectal excision, leaving this young patient with a neurogenic bladder and permanent colostomy. Rectal bleeding is the more common indication for acute resection, as in case 9 (*Table 1*). At laparotomy in this patient, the entire large bowel and ileum were inflamed. Colonic lavage through the amputated appendix and on-table colonoscopy, as described for other causes of major rectal bleeding[13], were of value in determining the extent of mucosal damage and to confirm that total colectomy was necessary (*Figure 2*). Minor bleeding from the rectum was controlled with packing, and bleeding from the ileostomy was controlled with iced-water lavage. Retention of the rectum is recommended unless it is severely damaged, and has allowed successful ileorectal anastomosis after 6 months in this patient.

Stricturing may occur late and although sometimes segmental[3] it is more typically left sided, as in case 8 (*Figure 1*). This may be due to the lateral position usually maintained after an enema[9]. If the right colon and anal canal are healthy, satisfactory results are obtained with left hemicolectomy, proctectomy and coloanal anastomosis as described by Cooke *et al.* in two cases[14], and performed in our case 8. The dissection of the rectum should stay close to the bowel wall, as in inflammatory bowel disease, to avoid pelvic nerve damage. With the development of modern stapling devices a low anastomosis can be effected by the double-stapling technique[15], which has been successfully employed in pouch–anal anastomosis after restorative proctocolectomy[16–18].

Toxic tribal enema within South Africa has been described in the northern[1,3,5,7,14], eastern[9] and now the southern regions. Deleterious additives can result in major gastrointestinal haemorrhage, peritonitis, renal failure or unexplained death. The *n'anga* enjoys considerable tribal authority, which needs to be reconciled with Western medicine. Traditional healers have been incorporated by the World Health Organization into Nigeria's health system and have been granted equal status with orthodox practitioners in Zimbabwe since independence. It remains a challenge to promote positive, and discourage harmful, cultural practices.

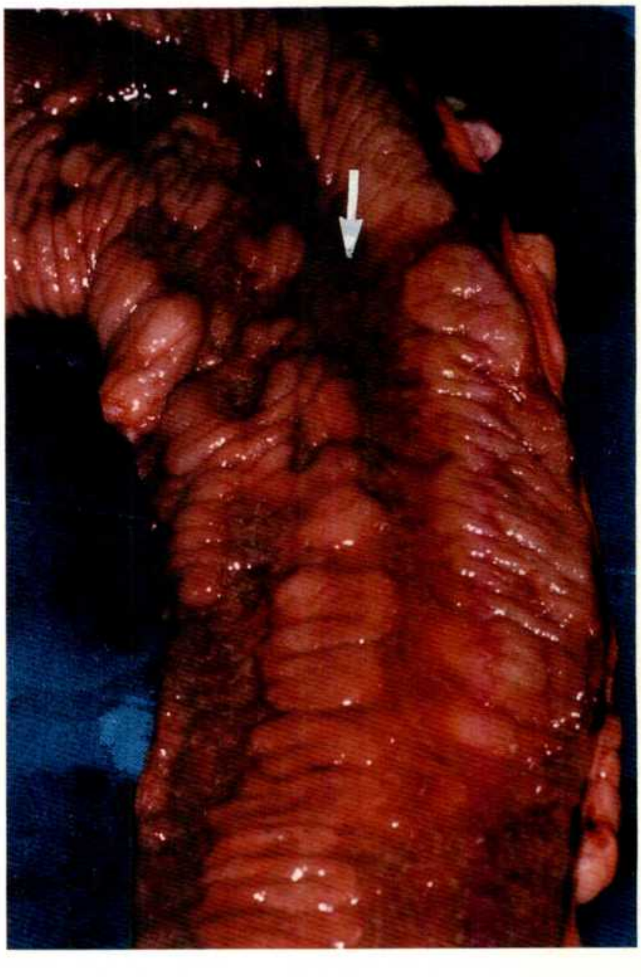

Figure 2 *Mucosal aspect of colectomy specimen (case 9) showing diffuse involvement with patchy deep ulceration (arrow)*

References

1. Bremner CG. Ano-rectal disease in the South African Bantu. 1. Bowel habit and physiology. *S Afr J Surg* 1964; **2**: 119–23.
2. Oettlé AG. Cancer in Africa, especially in regions south of the Sahara. *J Natl Cancer Inst* 1964; **33**: 383–7.
3. Segal I, Solomons A, Mirwis J. Radiological manifestations of ritual-enema-induced colitis. *Clin Radiol* 1981; **32**: 657–62.
4. Bürhmann MV. Witchcraft, witchcraft beliefs and the black people of South Africa. *S Afr Med J* 1985; **68**: 668–71.
5. Segal I, Ou Tim L. The witchdoctor and the bowel. *S Afr Med J* 1979; **56**: 308–10.
6. Segal I, Ou Tim L, Hamilton DG *et al.* Ritual-enema-induced colitis. *Dis Colon Rectum* 1979; **22**: 195–9.
7. Oettlé GJ, Segal I. Bowel function in an urban black African population. *Dis Colon Rectum* 1985; **28**: 717–20.
8. Hutchings A, Terblanche SE. Observations on the use of some known and suspected toxic Liliiflorae in Zulu and Xhosa medicine. *S Afr Med J* 1989; **75**: 62–9.
9. Young WS. Herbal-enema colitis and stricture. *Br J Radiol* 1980; **53**: 248–9.
10. Wood R, Mills P, Knobel GJ *et al.* Acute dichromate poisoning after use of traditional purgatives. *S Afr Med J* 1990; **77**: 640–2.
11. Wright JP, Froggatt J, O'Keefe EA *et al.* The epidemiology of inflammatory bowel disease in Cape Town 1980–1984. *S Afr Med J* 1986; **70**: 10–15.
12. Bader TF. Acute renal failure after chromic acid injection. *West J Med* 1986; **144**: 608–9.
13. Scott HJ, Lane IF, Glynn MJ *et al.* Colonic haemorrhage: a technique for rapid intra-operative bowel preparation and colonoscopy. *Br J Surg* 1986; **73**: 390–1.
14. Cooke SAR, Hamilton DG, Gritzman MCO. Transanal anastomosis in the treatment of low rectal strictures due to tribal enemas. *S Afr Med J* 1978; **54**: 769–72.
15. Knight CD, Griffen FD. An improved technique for low anterior resection of the rectum using the EEA stapler. *Surgery* 1980; **88**: 710–14.
16. Johnston D, Holdsworth PJ, Nasmyth DG *et al.* Preservation of the entire anal canal in conservative proctocolectomy for ulcerative colitis: a pilot study comparing end-to-end ileoanal anastomosis without mucosal resection with mucosal proctectomy and endoanal anastomosis. *Br J Surg* 1987; **74**: 940–4.
17. Williams NS, Marzouk DEMM, Hallan RI *et al.* Function after ileal pouch and stapled pouch–anal anastomosis for ulcerative colitis. *Br J Surg* 1989; **76**: 1168–71.
18. Kmiot WA, Keighley MRB. Totally stapled restorative proctocolectomy. *Br J Surg* 1989; **76**: 961–4.

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549–553

Myectomy reduces ileal motility after ileoanal anastomosis

The hypothesis tested was that myectomy of the distal ileum would produce a long-lasting decrease in ileal motility, and so render single-lumen ileum more suitable for use as a rectal substitute in the course of restorative proctocolectomy, without the need for a pelvic ileal reservoir. Ileal motility, both spontaneous and in response to intraluminal volatile fatty acids (VFA), was studied after proctocolectomy in 25 female adult beagles, at least 6 months after ileoanal anastomosis alone (IAA, $n=6$*), IAA with myectomy (*$n=8$*), IAA with myectomy and an ileal valve (*$n=5$*) or IAA with a duplicated (J) ileal reservoir (*$n=6$*). VFA were found to stimulate ileal motility significantly in each group. Myectomy significantly reduced the number of ileal contractions (*$P<0{\cdot}01$*), the mean amplitude of contractions (*$P<0{\cdot}05$*) and the motility index (*$P<0{\cdot}01$*). The addition of the valve to myectomy made no significant difference.*

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Restorative proctocolectomy with some type of pelvic ileal reservoir is now widely used in the elective surgical treatment of patients with ulcerative colitis and familial adenomatous polyposis[1]. By increasing the capacity and compliance of the distal ileum and by weakening its peristaltic drive, the reservoir leads to better clinical results than can be achieved by the use of single-lumen ileum[2]. However, such reservoirs have disadvantages of their own: they can be tedious to construct, can contribute to postoperative morbidity, may empty inefficiently, and sometimes give rise to troublesome episodes of 'pouchitis'.

Ileoanal anastomosis (IAA) without a reservoir yields unsatisfactory clinical results, both because of the lack of storage capacity in the distal ileum and because high pressure waves in the ileum may lead to excessive frequency of bowel action and even incontinence.

An attempt has therefore been made to create an acceptable substitute for normal rectum, without a conventional reservoir, by weakening the muscular wall of the distal ileum by means of myectomy. We and others have previously reported that this procedure increases the compliance and capacity of the ileum and yields functional results in dogs comparable with those observed after construction of a duplicated ileal reservoir[3–6]. In this paper, the motility characteristics of single-lumen ileum are reported, with and without myectomy, at rest and in response to intraluminal infusion of volatile fatty acids (VFA), which are known to stimulate ileal motility[7]. The effect of myectomy was compared with that of an artificial valve designed to slow intestinal transit and of a duplicated (J) ileal reservoir.

Methods

Operative procedures

The operations have been described in detail previously[3]. Briefly, 36 female adult beagles were allotted randomly to undergo one of four operative procedures:

1. Total proctocolectomy with IAA. The ileum was transected immediately proximal to the ileocolic valve and the rectum was transected at the anorectal line.
2. Total proctocolectomy and IAA with two myectomies, each 15 cm in length and about 1 cm in width. The myectomies began immediately above the IAA (*Figure 1*).
3. Total proctocolectomy with IAA, two myectomies and an ileoileal valve[8] which was constructed immediately proximal to the myectomized ileum. The valve was fashioned by excision of a 2·5-cm width of outer, longitudinal muscle. The inner, circular muscle was preserved. Apposition of the cut edges thus created a flap valve with a central core of circular muscle.
4. Total proctocolectomy with IAA and a duplicated J reservoir[9]. The J reservoir was constructed in a standard fashion with two 10-cm lengths of ileum anastomosed side to side.

Each IAA was constructed about 2 cm above the anocutaneous junction by means of a 21-mm Ethicon (Ethicon Ltd., Edinburgh, UK) stapling device. No rectal mucosectomy was carried out. A defunctioning ileostomy was not employed.

Experimental procedures

The studies of ileal motility were carried out in 30 dogs, at least 6 months (range 6–9 months) after operation. Each animal was in good health, well nourished and normally hydrated. The studies were completed successfully, however, in only 25 dogs (IAA, $n=6$; IAA with myectomy, $n=8$; IAA plus myectomy plus valve, $n=5$; IAA with J pouch, $n=6$) because five dogs proved uncooperative.

The dogs fasted for 18 h and were then placed in a modified Pavlov sling, in which they had been trained to stand patiently. A lubricated microtransducer catheter (Gaeltec Ltd., Dunvegan, Isle of Skye, UK), equipped with four microtransducers, each 5 cm apart, and a central perfusion channel, was advanced gently through the anal canal and positioned so that one microtransducer was in the anal canal at the point of maximum resting anal pressure as determined by the station pull-through technique, while the other three were in the 'neorectum'. The catheter was connected via a Gaeltec amplifier to a multichannel chart recorder (5041, Ormed Ltd., Welwyn Garden City, UK) with a chart speed of 6 cm/min.

The basal pattern of fasting motility was recorded for 45 min (period 1). The presence of the dog's handler helped to keep the dog calm and relatively stationary; artefacts on the motility trace caused by movement were immediately identified and excluded from subsequent analysis.

When period 1 had been completed, ileal motility was recorded for a further 30 min (period 2). Solutions of either normal saline (154 mmol/l) or VFA were infused through the central perfusion channel of the Gaeltec catheter.

Preliminary experiments confirmed that motility patterns were unaltered by distension up to a maximum of 20 ml[7]. Each solution was therefore instilled at a volume of 15 ml at 40°C, administered as 15-ml boluses over 30 s at 5-min intervals. Each dog received one bolus of saline and five boluses of VFA. Each dog underwent a single study in which the total period of recording was 75 min. Repeat evaluations at a later date were not performed.

The test solution of VFA was made up to a fatty acid concentration of 108 mmol/l containing by proportion 66 per cent acetic acid, 24 per cent propionic acid and 10 per cent butyric acid (BDH, Speke, Liverpool, UK) as described by others[7]. Its pH was 6·8 and osmolality was 285 mosmol/kg. This solution contains VFA in similar proportions to those found in the caecum of dogs[10]. The solution was made up freshly each week and stored at 4°C.

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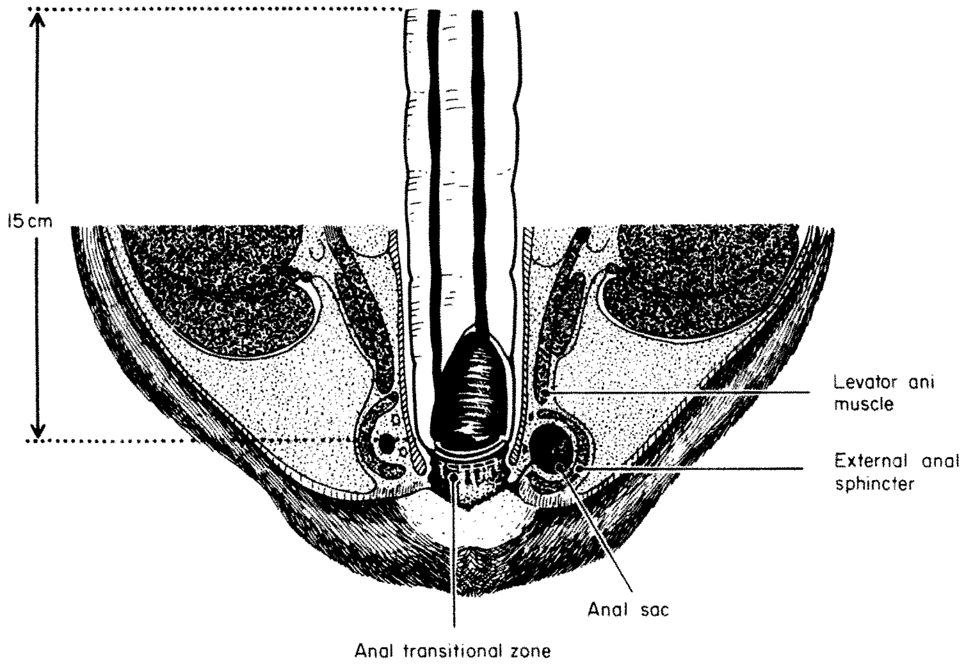

Figure 1 *Ileoanal anastomosis with myectomy 15 cm in length*

Definitions and statistical analysis

Phasic contractions were defined as fluctuations in intraluminal pressure of >10 mmHg that reached a peak and returned to baseline levels within the duration of one slow wave[11]. The intrinsic frequency of slow waves in the ileum of the dog is 10–12/min[12].

Tonic contractions were defined as increases in intraluminal pressure of >10 mmHg that remained elevated during two or more consecutive slow waves.

Rhythmical phasic activity was defined as sequences of regular phasic waves with a total duration of >30 s. The frequency of the phasic waves was equal to that of slow waves in the same region[13].

Proximal propagated contractions were defined as high amplitude waves (>60 mmHg) of duration >12 s and which migrated distally over at least two channels.

Discrete clustered contractions were defined as bursts of phasic waves of amplitude of >40 mmHg and lasting for at least 60 s.

A positive response to infusion of VFA was recorded if proximal propagated or discrete clustered contractions were registered within 60 s of instillation of the solution.

The motility index was defined as the sum of the products of amplitude and duration of each contraction in period 1 (mmHg × min) (Reference 14).

Each of the recordings of ileal motor activity was analysed by direct visual inspection. All pressure waves with an amplitude of >15 mmHg were noted and included in the analysis. Pressure waves of <15 mmHg were excluded because it was difficult to distinguish these from respiratory excursions.

All grouped data were expressed as medians and interquartile ranges. The groups were compared by means of the Mann–Whitney *U* test[15].

Results

Qualitative analysis

Recognizable patterns of ileal motility were recorded in each of the 25 dogs. The recordings in period 1 were largely typical of phase I or phase II of the mechanical equivalent of the interdigestive myoelectrical cycle, with prolonged periods of quiescence or occasional sporadic spikes respectively. The apparent passage of phase III or the 'front' of the cycle was recorded, however, at least once in each group of dogs. Although such events were uncommon, they were usually associated with the passage *per anum* of small amounts of semisolid stool.

The recordings obtained in dogs with IAA alone, without myectomy, were characterized by apparently random bursts of tonic and phasic contractions (*Figure 2a*) and, less frequently, by rhythmical phasic activity (*Figure 2b*). This rhythmical phasic activity had a median duration of 58 s (interquartile range 44–185 s) and a frequency of 10·3 cycles/min. In contrast, the recordings obtained in dogs which had undergone IAA with myectomies showed long periods of inactivity (*Figure 3*).

Quantitative analysis

Quantitative analysis of the motility recordings showed that there were significant differences between dogs with IAA alone and the other three operative groups. The total number of tonic and phasic contractions, the median amplitude of the contractions, and the motility index were all significantly greater in dogs with IAA alone than in dogs with IAA and myectomy, IAA plus myectomy plus valve, or J pouch (*Table 1*).

Responses to volatile fatty acids

A positive response to the infusion of VFA was easy to recognize. Characteristic motor patterns, usually discrete clustered contractions, were recorded either towards the end or promptly after completion of the instillation of VFA (*Figure 4*). Positive responses occurred with similar frequency in each of the four groups and their magnitude also did not differ significantly (*Table 2*). Earlier instillations were somewhat more likely to produce a positive response than later instillations. Instillation of normal saline never elicited a positive response.

Discussion

The principal findings were that the motility of single lumen ileum after fasting is reduced by myectomy to the level that is found in the duplicated ileal (J) reservoir. That terminal ileum responds to the presence of VFA instilled into its lumen was also confirmed.

The reduction in motility of ileum demonstrated in this study lends further support to the idea that myectomized ileum might be used as an alternative to a pelvic ileal reservoir in the course of restorative proctocolectomy[4–6]. The use of IAA without a reservoir has been abandoned in most centres because its results compare unfavourably with those of pelvic reservoirs; bowel frequency is greater, nocturnal incontinence is more common, and thus the incidence of failure is greater than in patients with reservoirs[2]. The pelvic ileal reservoir is more distensible and capacious than single-lumen ileum. In addition, phasic changes in ileal pressure in patients with a straight IAA are significantly greater than in patients with a pelvic ileal reservoir[16]. Whereas normal rectum responds to distension by relaxation of its smooth muscle, terminal ileum contracts strongly. The high pressures generated by ileum can thus exceed the resting pressure of the anal sphincter and cause faecal leakage. Such instances tend to be more common at night since voluntary contraction of the anal sphincter during the day is able to counteract the high pressure waves and reduce the incidence of leakage. The reduction in ileal motility after myectomy may therefore result in a better functional outcome than that seen after IAA alone.

The duration of assessment of ileal motility in this study (75 min) was relatively short compared with the periods of observation used by others. Studies that have recorded ileal motility for longer periods have usually done so either in ileocolonic loops[7], which avoid the need for a transanal probe, or have used sedation or anaesthesia to obtain prolonged recordings[14]. Extraluminal strain gauge transducers[17] or silver monopolar electrodes sutured to the serosal surface[18] could provide recordings of ileal motility for much longer periods. Ileal motility studied in patients after ileal pouch–anal anastomosis has usually involved nasointestinal intubation[19], although some have successfully studied small numbers of patients with manometric catheters passed *per anum* into the distal ileum[20]. Such patients would tolerate the catheters for 5 h or more. Our dogs were not so co-operative.

Continuous recordings of motility in conscious dogs from ileal looops for several hours[7] or from intact ileum for several weeks by means of implanted strain gauge force transducers[21] have demonstrated repeating cycles of the mechanical equivalent of the interdigestive myoelectric complex, which

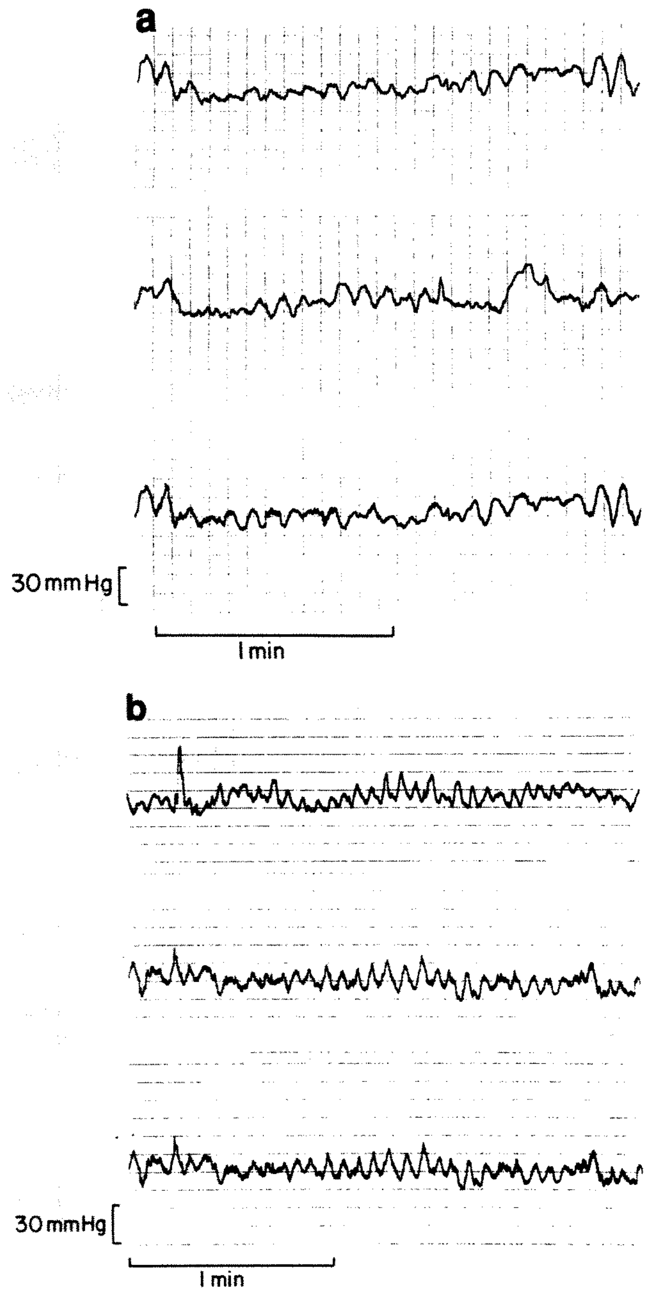

Figure 2 *Recordings from ileum of dogs which had undergone ileoanal anastomosis alone showed irregular bursts of phasic and tonic contractions* **a** *and, less commonly, episodes of rhythmical phasic activity* **b**

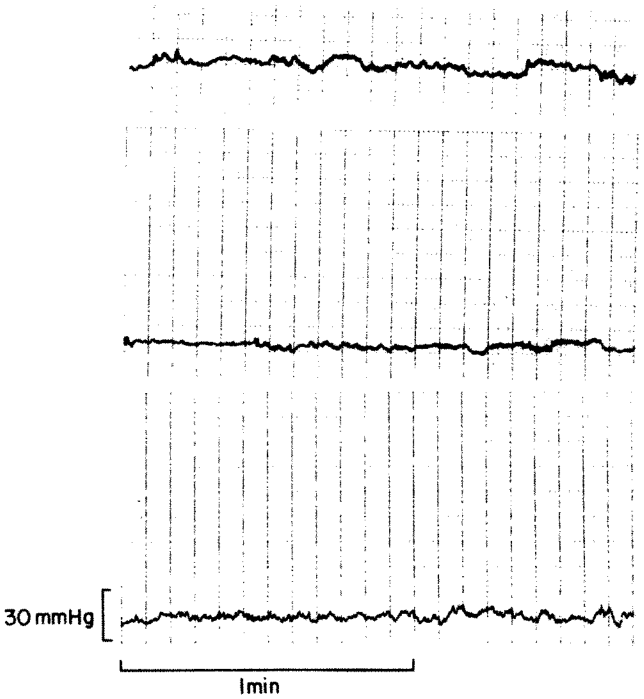

Figure 3 *Recordings following ileoanal anastomosis with myectomy were typically quiescent*

Table 1 *Quantitative analysis of motility recordings from period 1*

	IAA ($n=6$)	IAA with myectomy ($n=8$)	IAA +myectomy+valve ($n=5$)	IAA with J pouch ($n=6$)
No. of contractions in period 1 (45 min)	58* (34–75)	8 (4–22)	28 (16–36)	15 (7–20)
Amplitude of contractions (mmHg)	80† (68–88)	53 (41–57)	57 (51–65)	55 (36–63)
Motility index (mmHg × min)	600* (188–910)	80 (65–138)	151 (69–179)	122 (23–135)

Values are medians with interquartile ranges in parentheses. IAA, ileoanal anastomosis; * $P<0{\cdot}01$, IAA compared with each of the other three operative groups; † $P<0{\cdot}05$, IAA compared with each of the other three operative groups; IAA + myectomy *versus* IAA + J pouch, no significant difference; IAA + myectomy *versus* IAA + myectomy + valve, no significant difference repeats every 90–120 min and migrates along the length of the small bowel. Hence, the relatively short period used for each of our tests prevented demonstration of the full cycle in any one dog. Furthermore, the results may have been biased by the occurrence of a greater proportion of phase III activity, characterized by intense bursts of rhythmical mechanical events, in one or more of the four operative groups. Previous experience with these dogs suggested, however, that it would be impossible to keep them relaxed and stationary for longer than 60–90 min. Indeed, it was not possible to obtain motility recordings in five dogs.

It is unlikely that these features of the recordings could be the result of artefact. Intraluminal transducers were used in preference to the more popular systems that employ continuously perfused open-tip catheters because the microtransducer system was found to be more convenient and is portable. In theory, miniature pressure transducers should record small changes in pressure more accurately than perfused systems because distortion of only part of the circuit is necessary to generate a signal[22]. Similar patterns of motility to those observed have been recorded in dogs by means of intraluminal sensors, extraluminal strain gauges and serosal electrodes[11,13,23]. Interference with the recording patterns caused by movement of the dogs while the probe was *in situ* was readily identified at the time of the study and excluded. The influence of the presence of ileal content was not taken into account although the tests were carried out only after each dog had emptied her neorectum. No mechanical means of emptying the bowel were used. It is thus possible that the semisolid content within the neorectum could have dampened the tonic and phasic contractions observed in some of the dogs. One could speculate that this would be more likely to occur in dogs with a more capacious neorectum, i.e. in all of the dogs except those with IAA alone.

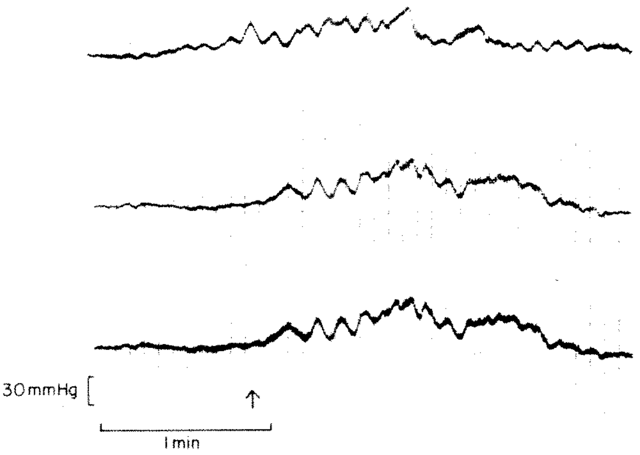

Figure 4 *Instillation of volatile fatty acids (VFA) elicited well defined bursts of activity in each of the four operative groups. (Arrow denotes time of cessation of VFA instillation)*

VFA regularly stimulated ileal contractions and produced high-amplitude pressure waves. This was not observed with saline. The pressure generated not infrequently exceeded that measured in the anal canal and was then associated with minor leakage around the catheter. This was presumably not the result of volume distension because similar volumes of normal saline did not elicit a similar response. The concentrations of VFA used were dictated by those reported by others[7] to produce similar contractions in isolated ileocolonic loops. There were no significant differences in the qualitative or quantitative responses to the instillations when the four operative groups were compared.

The amplitude and duration of contractions in response to VFA infusions were not greater in the straight IAA group than the other three operative groups. This is perhaps surprising in view of the marked differences in ileal motility recorded at rest. The concentrations of VFA used in the instillate were originally determined by others by gas–liquid chromatography of stool from dogs with ileorectostomies[7]. The values were similar but not identical to those seen in stool from canine caecum[10]. The concentration of VFA in stool from dogs with IAAs has not been determined as far as we are aware. It may be that our technique involves the introduction of supraphysiological concentrations into the distal ileum and hence elicits more forceful contractions than would normally be present. Nevertheless, the results of these experiments allow the conclusion that, although myectomy reduced ileal motility at rest, no such reduction occurred in response to VFA infusion.

A positive response to VFA was less likely to be recorded with later administrations, suggesting that the ileum may become relatively insensitive to VFA as more boluses are given. VFA do not stimulate motility in canine colon[24] and the colon is a site where they are produced physiologically. It has been suggested that the contractile response of the ileum to VFA is part of the mechanism that prevents coloileal reflux[7]. The concentration of VFA in the effluent from pelvic ileal reservoirs is greater than the concentration of VFA in the effluent from ileostomies[25]. It might be expected that prolonged exposure to VFA would desensitize the ileum and reduce the response to VFA instillation. Such a desensitization would presumably be more likely to occur if the ileum were to undergo colonic metaplasia. Each of these experiments took place between 6 and 9 months after operation. The response to VFA may be less marked if tested at a later stage.

Attempts to alter motility and slow transit by means of an artificial valve in the ileum yielded disappointing results. It has previously been shown that the addition of an ileoileal valve proximal to the myectomized ileum does not slow intestinal transit or improve the functional result obtained with myectomy alone[3]. The present studies of ileal motility in dogs with IAA plus myectomy plus valve showed an increased motility index

Table 2 *Effect of volatile fatty acids on ileal motility*

	IAA ($n=6$)	IAA with myectomy ($n=8$)	IAA + myectomy + valve ($n=5$)	IAA with J pouch ($n=6$)
No. of positive responses to normal saline	0	0	0	0
No. of positive responses to VFA infusions per dog (maximum = 5)	3 (0·5–3·8)	3 (3·0–3·0)	4 (2·0–4·8)	3 (0–3·0)
Mean amplitude of contractions (mmHg)	65 (45–66)	50 (45–55)	60 (48–66)	60 (45–75)

Values are medians with interquartile ranges in parentheses. IAA, ileoanal anastomosis; VFA, volatile fatty acids. 'Positive responses' are bursts of high amplitude contractions (>40 mmHg) which last for at least 12 s and occur within 60 s of infusion of VFA. No significant differences in response to VFA were found between the four groups and number of ileal contractions compared with IAA plus myectomy alone, but these differences did not reach statistical significance. The valve did not appear to disturb ileal motility. Complete transection of the small bowel disturbs the myogenic and intrinsic neutral activity within the bowel wall, which leads to a loss of coupling of slow waves and consequently a loss of stimulation of bowel segments distal to the anastomosis by proximal oscillations of a higher frequency. The removal of the outer longitudinal muscle layer in the construction of the ileal valve in this study is unlikely to have influenced the propagation of slow waves significantly. If such valves are to have any application to surgery in humans, their design will have to be different from that used here.

Transverse section of taenia coli in rabbits has been reported to reduce the activity and amplitude of colonic contractions compared with that observed in adjacent sections of bowel without myotomy[14]. In humans, sigmoid myotomy has been advocated for the treatment of diverticular disease[26] and, although the early results were promising, the procedure was abandoned when it became clear that the sites of the myotomy underwent fibrosis with a deterioration in the functional result[27], presumably because of healing or closure of the gap in the muscle. Myectomy, as opposed to myotomy, may have the advantage of preventing such healing and may thus produce better long-term results. The reduction in motility may be partly due to the reduction in the mass of smooth muscle within the ileal segment used to form a neorectum.

The long-term effects of myectomy on motility and functional outcome remain to be determined. The effects have not been studied beyond 12 months[28,29]. In the longest reported study the capacity of the ileal reservoir with myotomy remained two to three times that of control ileum at 12 months[4]. Furthermore, the frequency of bowel action was similar to that observed in animals with a J pouch, with a significant decrease between 6 and 12 months after operation. The ability of the myotomized ileum to absorb water and sodium and to secrete potassium continued to improve up to 12 months.

In conclusion, we compared the motility of ileum used as a neorectum in four operative procedures in an animal model. Myectomy reduced the frequency and amplitude of contractions within the ileum to a level comparable with that seen in the duplicated (J) pelvic ileal reservoir. Ileum continued to respond to the presence in its lumen of VFA after IAA with and without myectomy and when fashioned into a reservoir.

Acknowledgements

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References

1. Williams NS. Restorative proctocolectomy is the first choice elective surgical treatment for ulcerative colitis. *Br J Surg* 1989; **76**: 1107–8.
2. Taylor BM, Beart RW, Dozois RR, Kelly KA, Phillips SF. Straight ileoanal anastomosis v. ileal pouch–anal anastomosis after colectomy and mucosal proctectomy. *Arch Surg* 1983; **118**: 696–701.
3. Sagar PM, Holdsworth PJ, Salter GV, King RFGJ, Johnston D. Single lumen ileum with myectomy: an alternative to the pelvic reservoir in restorative proctocolectomy. *Br J Surg* 1990; **77**: 1030–5.
4. O'Malley VP, Keyes DM, Cannon JP, Postier RG. Longitudinal ileal myotomy: a new reservoir for use with ileoanal anastomosis. *Curr Surg* 1985; **42**: 113–17.
5. Imhof M. *In vitro* untersuchungen zur intestinalen motorik bei entzundlichen darmerkrankungen und neue techniken der chirurgischen therapie. MD thesis, University of Wurzburg, 1988.
6. Accarpio G, Scordamaglia R, Mignone D, Pozzatti A, Accarpio V. Total colectomy with ileo-anal anastomosis and myotomy in the treatment of patients with colonic diseases. *Coloproctocology* 1983; **5**: 263–5.
7. Kamath PS, Hoepfner MT, Phillips SF. Short-chain fatty acids stimulate motility of the canine ileum. *Am J Physiol* 1987; **253**: G427–33.
8. Grosfeld JL, Cooney DR, Jesseph JE. Experimental ileocecal valve replacement in puppies. *Surg Forum* 1974; **25**: 364–5.
9. Utsunomiya J, Iwama T, Imajo M,*et al.* Total colectomy, mucosal proctectomy and ileo-anal anastomosis. *Dis Colon Rectum* 1980; **23**: 459–66.
10. Banta CA, Clemens ET, Krinsky MM, Shefy BE. Sites of organic acid production and patterns of digestive movement in the gastrointestinal tract of dogs. *J Nutr* 1979; **109**: 1592–1600.
11. Quigley EMM, Phillips SF, Dent J, Taylor BM. Myoelectric activity and intraluminal pressure of the canine ileocolonic sphincter. *Gastroenterology* 1983; **85**: 1054–62.
12. Phillips SF. Normal small bowel motility. In: Kumar D, Gustavsson S, eds. *An Illustrated Guide to Gastrointestinal Motility*. Chichester: John Wiley and Sons, 1988: 187–206.
13. Quigley EMM, Phillips SF, Dent J. Distinctive patterns of interdigestive motility at the canine ileocolonic junction. *Gastroenterology* 1984; **87**: 836–44.
14. Johnson AG. The effect of transverse section of the taenia coli (taeniamyotomy) on intracolonic pressures in the rabbit. *Scand J Gastroenterol* 1972;**7**: 321–7.
15. Cohen L, Halliday M. *Statistics for Social Scientists*. London: Harper and Row, 1982.
16. Taylor BM, Cranley B, Kelly KA, Phillips SF, Beart RW, Dozois RR. A clinico-physiological comparison of ileal pouch–anal and straight ileoanal anastomoses. *Ann Surg* 1983; **198**: 462–8.
17. Schemann M, Ehrlein H-J. Mechanical characteristics of phase II and phase III of the interdigestive migrating motor complex in dogs. *Gastroenterology* 1986; **91**: 117–23.
18. Kruis W, Azpiroz F, Phillips SF. Contractile patterns and transit of fluid in canine terminal ileum. *Am J Physiol* 1985; **249**: G264–70.
19. Stryker SJ, Borody TJ, Phillips SF, Kelly KA, Dozois RR, Beart RW. Motility of the small intestine after proctocolectomy and ileal pouch–anal anastomosis. *Ann Surg* 1985; **201**: 351–6.
20. Heppell J, Pemberton JH, Kelly KA, Phillips SF. Ileal motility after endorectal ileoanal anastomosis. *Surg Gastroenterol* 1982; **1**: 123–7.
21. Itoh Z, Takeuchi S, Aizawa I, Takayanagi R. Characteristic motor activity of the gastrointestinal tract in fasted conscious dogs measured by implanted force transducers. *Dig Dis* 1978; **23**: 229–38.
22. Gustavsson S, Tucker R. Manometry. In: Kumar D, Gustavsson S, eds. *An Illustrated Guide to Gastrointestinal Motility*. Chichester: John Wiley and Sons, 1988: 67–76.
23. Quigley EMM, Borody TJ, Phillips SF, Wienbeck M, Tucker RL, Haddad A. Motility of the terminal ileum and ileocecal sphincter in healthy humans. *Gastroenterology* 1984; **87**: 857–66.
24. Flourie B, Richter H, Phillips SF. Cyclic motility in the canine colon: responses to feeding and perfusion. *Gastroenterology* 1986; **90**: 1418 (Abstract).
25. Nasmyth DG, Godwin PGR, Dixon MF, William NS, Johnston D. Ileal ecology after pouch–anal anastomosis or ileostomy. *Gastroenterology* 1989; **96**: 817–24.
26. Reilly M. Sigmoid myotomy. *Br J Surg* 1966; **53**: 859–63.
27. Smith AN, Giannakos V, Clarke S. Late results of colomyotomy. *J R Coll Surg Edinb* 1971; **16**: 276–86.
28. Turnage RH, Coran AG, Drongowski RA. The value of intestinal myotomy and myectomy in improving the reservoir capacity of the endorectal pull-through. *Ann Surg* 1990; **211**: 463–9.
29. Aly A, Fonkalsrud EW. Contruction of ileal reservoir with longitudinal ileal myotomy. *Am Surg* 1988; **54**: 475–8.

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Risks of leaving the gallbladder *in situ* after endoscopic sphincterotomy for bile duct stones

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There is controversy concerning the subsequent clinical course of patients whose gallbladder is left in situ *following successful endoscopic removal of stones from their common bile ducts. A total of 191 patients (median age 76 years) were reviewed between 12 and 100 months (mean 38 months) after endoscopic sphincterotomy. Ten patients (5·2 per cent) had symptoms requiring cholecystectomy which was uneventful, nine in the first year. Cholangitis at presentation or failure to fill the gallbladder by endoscopic retrograde cholangiography were not helpful in identifying these patients. Forty-nine (25·6 per cent) patients died during the review period from non-biliary pathology (usually cardiovascular). Elective cholecystectomy is not required in elderly patients with symptomatic bile duct stones if the common bile duct can be cleared of stones after endoscopic sphincterotomy.*

Endoscopic sphincterotomy is a safe and effective method for the management of symptomatic common duct stones in patients with an intact gallbladder[1–5], but there are three areas of controversy. What percentage of patients will subsequently require cholecystectomy because of the development of acute cholecystitis and its complications; is there a greater postoperative mortality in these patients than in those undergoing elective cholecystectomy; and are there risk factors which can be used to identify patients likely to develop symptoms or complications related to the retained gallbladder?

Patients and methods

Between July 1981 and December 1988, a total of 218 patients (89 men and 129 women) with intact gallbladders were seen with symptoms related to the presence of common duct stones. Of these, 81 were the subject of a previous report[5]; 151 (69·3 per cent) were specifically referred for endoscopic management from other hospitals in the north-west of England and Wales. Their ages ranged from 28 to 94 years (median 76 years), 16 patients (7·3 per cent) being under 60 years and 86 (39·5 per cent) over 80 years.

The main presenting symptoms were jaundice in 131 (60 per cent) patients, cholangitis in 38 (17·4 per cent), pain in 34 (15·6 per cent), and pancreatitis in 15 (6·9 per cent); many patients presented with more than one symptom. No patient exhibited clinical features of gallbladder inflammation at the time of endoscopic sphincterotomy. Intravenous antibiotics, most recently mezlocillin 2 g, were given before endoscopic retrograde cholangiopancreatography (ERCP).

ERCP was performed using Olympus JF1T, JF1T10 and TJF10 duodenoscopes (Olympus Keymed, Southend, UK). Attempts were made not to overfill the biliary tree on cholangiography and no specific attempt was made to opacify the gallbladder. Endoscopic sphincterotomy was performed using a Classen-Demling sphincterotome or a fistulotomy knife when necessary with an Erbotom diathermy unit. Stones were cleared using baskets or balloon catheters where possible. In addition, a combination of pernasal catheters and duct perfusion with 5 per cent dextrose, stents, extracorporeal shock wave lithotripsy and an Olympus BML-3Q mechanical lithotripter were used to clear the ducts. If duct clearance was not achieved at the first attempt the common duct was drained with either a pernasal catheter or a biliary stent.

Current health status was ascertained directly from the patients and from the general practitioner by questionnaire. Cause of death was established either from hospital records, from the general practitioner or the Registrar of Births, Marriages and Deaths.

Results

Endoscopic and radiological features

Dilated bile ducts were present in 190 (87·2 per cent) patients and the gallbladder filled at ERCP in 123 (56·4 per cent) patients. Stones in the gallbladder, identified by a variety of radiological techniques, were present in 150 (68·8 per cent)[2] patients. Endoscopic sphincterotomy was achieved in 211 (96·8 per cent) of 218 patients (*Figure 1*) and failed in seven (3·2 per cent). Causes of failure were previous Polya-gastrectomy in three patients, duodenal diverticular in two, and there were two patients in whom the papilla could not be found despite more than one attempt to locate it.

Common duct clearance

The common duct was cleared of stones in 193 (88·5 per cent) of the 218 patients and this was confirmed endoscopically in all cases. In 25 (11·5 per cent) patients duct clearance was unsuccessful (*Table 1*). In seven of these 25 patients endoscopic

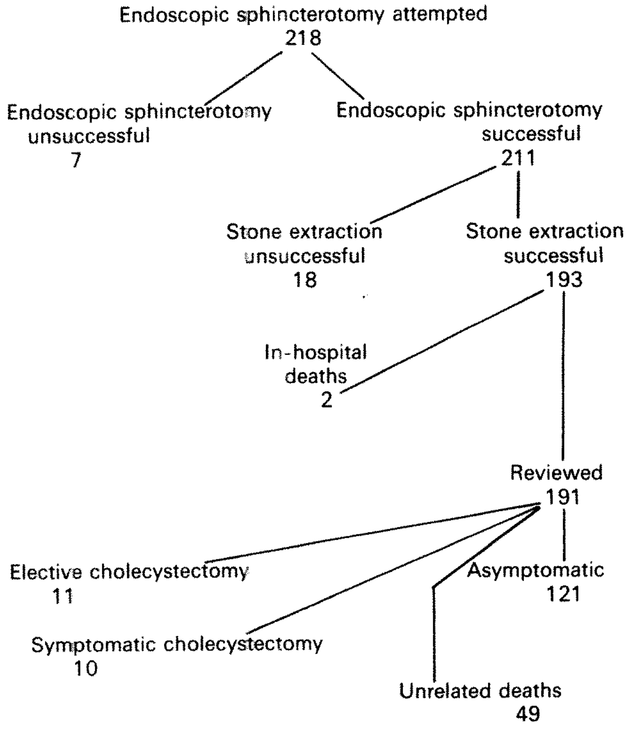
Endoscopic sphincterotomy attempted
218
Endoscopic sphincterotomy unsuccessful
7
Endoscopic sphincterotomy successful
211
Stone extraction unsuccessful
18
Stone extraction successful
193
In-hospital deaths
2
Reviewed
191
Elective cholecystectomy
11
Asymptomatic
121
Symptomatic cholecystectomy
10
Unrelated deaths
49

Figure 1 *Clinical outcome of endoscopic sphincterotomy*

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sphincterotomy had not been possible. In 14 of the remaining 18 patients the stones were considered too large to be removed by endoscopic sphincterotomy. Two patients refused further ERCP having become asymptomatic. One patient underwent surgery in the hands of the referring clinician while awaiting repeat ERCP and one patient was lost to follow-up. Eighteen of the 25 patients in whom common duct clearance failed underwent cholecystectomy and choledocholithotomy during the same admission without mortality. Of the other seven, four were considered unfit and three discussed above refused ERCP or were lost to follow-up. Two of these seven patients developed recurrent jaundice and required surgery. One is asymptomatic at 12 months and four died of unrelated causes 6, 9, 12 and 36 months respectively after endoscopic sphincterotomy.

Complications

Immediate complications of endoscopic sphincterotomy occurred in 16 (7·6 per cent) of 211 patients (*Table 2*). Haemorrhage defined as a drop in haemoglobin concentration greater than 2g/dl occurred in seven patients, two requiring blood transfusion only. The other five underwent laparotomy and oversewing of the bleeding point, all five surviving the initial surgery. Two (1·0 per cent) patients died within 30 days of sphincterotomy. One patient, an 85-year-old woman, was transferred back to her referring unit and died 1 week later from recurrent bleeding, her physician deciding that further surgery was not warranted. The other patient who died was a 75-year-old man who presented with acute pancreatitis. The ducts were cleared but he developed a pancreatic abscess during the same admission and died. Five patients developed cholangitis, two pancreatitis and two suffered asymptomatic retroperitoneal perforation, all resolving with conservative treatment. No patient developed clinical features of acute cholecystitis within 30 days of endoscopic sphincterotomy.

Table 1 *Causes of failed duct clearance*

Cause of failure	No. of patients
Failed endoscopic sphincterotomy	7
Stones too large	14
Refused further ERCP	2
Lost to follow-up	1
Surgical impatience	1

ERCP, endoscopic retrograde cholangiopancreatography

Table 2 *Complications of endoscopic sphincterotomy in 211 patients*

Complication	No. of patients
Haemorrhage	7 (3·3)
Cholangitis	5 (2·4)
Pancreatitis	2 (1·0)
Retroperitoneal perforation	2 (1·0)

Values in parentheses are percentages

Follow-up

All 191 patients with a clear common bile duct following endoscopic sphincterotomy have been reviewed between 12 and 100 months (mean 38 months). Eleven asymptomatic patients had elective cholecystectomy performed by the referring surgeon. Six of these were under 60 years of age. In only one of these 11 patients was exploration of the common duct necessary, a single stone being removed. This duct was clear of stones at ERCP and presumably the stone had passed from the gallbladder. Ten patients required cholecystectomy for symptoms or complications related to the gallbladder calculi. Indications for surgery were acute cholecystitis in five patients, biliary colic in three, jaundice in one and dyspepsia in one. Gallbladder calculi were present in all ten patients when the initial ERCP was performed, but present in only seven at cholecystectomy. The three patients with an empty gallbladder at cholecystectomy were diagnosed as having either biliary colic or dyspepsia. It is possible that cholecystectomy could have been avoided in these three patients if ultrasound scanning had been performed and shown an empty gallbladder. In nine of the ten patients cholecystectomy was necessary in the first year of follow-up. The other cholecystectomy was performed 4 years after endoscopic sphincterotomy, the indication for surgery being dyspepsia. In all, 49 (25·6 per cent) of the 191 patients died during the review period. No death was from biliary disease and no patient suffered symptoms related to the biliary tract. Of the 191 patients, 121 (63·4 per cent) remain alive and well with their gallbladders *in situ*.

Discussion

Endoscopic sphincterotomy compares favourably with cholecystectomy and exploration of the common bile duct in comparable groups of patients[6–9], but the subsequent management of the retained gallbladder remains controversial.

Two recent publications have suggested that 18 per cent and 40 per cent of patients undergoing successful endoscopic choledocholithotomy will subsequently require cholecystectomy[10,11], but in the present series only ten (5·2 per cent) patients required cholecystectomy for symptoms. The results of ten published series of patients undergoing endoscopic sphincterotomy for removal of symptomatic bile duct stones in patients with intact gallbladders are are shown in *Table 3*[1–4,10–14]. In eight of the ten series with a minimum

Table 3 *Results of endoscopic sphincterotomy in patients with gallbladder* in situ

Author	Year	No. of patients	Mean age (years)	Mean follow-up (months)	Cholecystectomies no. (%)	Operative mortality no. (%)
Escourrou *et al.*[12]	1984	130	79	22	7 (5·4)	Nil
Davidson *et al.*[1]	1988	105	79	29	9 (8·6)	Nil
Siegel *et al.*[4]	1987	1272	73	?	133 (10·5)	4 (3·0)
Tanaka *et al.*[14]	1987	122	69	36	5 (4·1)	Not reported
Worthley and Toouli[11]	1988	20	80	9	8 (40)	3 (37·5)
Hansell *et al.*[10]	1989	101	80	24	18 (17·8)	Not reported
Vaira *et al.*[13]	1989	265	76	36	24 (9·0)	Not reported
Ingolby *et al.*[2]	1989	186	80	32	18 (9·7)	Nil
Cotton and Vallon[3]	1982	260	76	12–72	26 (10·0)	Not reported
Present series	1990	191	74	38	10 (5·2)	Nil
Total		2656			258 (9·7)	7 (2·7)

follow-up of 22 months, cholecystectomy for symptoms was necessary in less than 11 per cent of cases and in all ten series the mean rate for cholecystctomy was 9·7 per cent. In this series, nine of the ten patients requiring cholecystectomy did so within 1 year of endoscopic sphincterotomy, a similar finding to that of other series[10,12,14]. The subsequent development of cholecystitis from gallbladder calculi has been reported at an annual rate of 2–7·5 per cent in patients without duct stones[15,16]. Long-term follow-up in our series and others[14,17,18] has shown that the incidence of cholecystitis in the first year after endoscopic sphincterotomy is no greater than the predicted rate for all patients with gall stones and significantly less in subsequent years.

In this series the mortality of patients undergoing cholecystectomy for symptoms was nil. Apart from one very small series[11] with a mortality rate of 37·5 per cent, other reported mortality rates (*Table 3*) are similar to that for elective cholecystectomy in an aged population[19,20], and it is apparent that the mortality and requirement for cholecystectomy reported by Worthley and Toouli[11] is unrepresentative. In four of the reported series shown in *Table 3* there were no details concerning mortality of any subsequent cholecystectomy. In four of the remaining series there were no deaths in these very elderly patients. Overall there were seven deaths in 258 patients (2·7 per cent) undergoing cholecystectomy. In our series 49 (25·6 per cent) patients died during the review period from causes unrelated to the biliary tract, the vast majority from cardiovascular disease. From this and the collected data in *Table 3*, we believe that routine elective cholecystectomy is not warranted if the common duct can be cleared of stones after endoscopic sphincterotomy.

Attempts have been made to find risk factors that might identify those patients likely to develop complications from their retained gall stones. Cystic duct obstruction in particular[3,11,21] and cholangitis at presentation[1] have been suggested as risk factors. In our series the gallbladder did not fill in 88 (41·7 per cent) patients, a similar percentage to that found in the ten patients who required cholecystectomy for symptoms (*Table 4*). Non-filling of the gallbladder during biliary excretion scintigraphy in patients who have had endoscopic sphincterotomy has recently been described[22] and the authors suggested that stagnant bile may predispose to chronic infective changes or carcinoma in the gallbladder. Our results up to 100 months after endoscopic sphincterotomy do not suggest that this is likely in the aged population in whom this procedure is usually undertaken. Thirty-eight patients (17·5 per cent) presented with cholangitis. Only two of these required subsequent cholecystectomy. Like others we have not found cystic duct obstruction[1,10] or cholangitis at presentation[10] helpful in identifying patients who will require subsequent cholecystectomy. All ten patients undergoing cholecystectomy for symptoms had gallbladder calculi at presentation but even this was not a positive risk factor for the development of complications from the retained gallbladder.

As in the series of Davidson *et al.*[1], none of the 15 patients with acute pancreatitis and an intact gallbladder has had a further attack. After an attack of acute biliary pancreatitis, cholecystectomy is usually advocated[23–26]. Although one patient in our series died of a pancreatic abscess our results would support the view that endoscopic sphincterotomy alone may have a role in elderly patients with acute biliary pancreatitis.

Table 4 *Impact of potential risk factors on the need for cholecystectomy*

	Patients at risk (*n* = 211)	Cholecystectomy (*n* = 10)	Fisher's exact test *P*
Non-functioning gallbladder	88 (41·7)	4 (40)	1·000
Cholangitis at presentation	38 (18·0)	2 (20)	1·0000
Gallbladder stones at presentation	150 (71·1)	10 (100)	0·065

Values in parentheses are percentages

To minimize the risks of biliary sepsis after endoscopy, all patients undergoing endoscopic sphincterotomy for symptomatic common duct stones and an intact gallbladder should have appropriate prophylactic intravenous antibiotics. An attempt should be made to clear the duct immediately, and if this is not possible biliary drainage should be ensured with either a pernasal catheter or a stent.

In conclusion: (1) elective cholecystectomy is not warranted in elderly patients with symptomatic bile duct stones if the common duct can be cleared of stones after endoscopic sphincterotomy, and (2) neither cystic duct obstruction nor cholangitis at presentation are predictors of further symptoms or complications from the retained gallbladder.

References

1. Davidson BR, Neoptolemos JP, Carr-Locke DL. Endoscopic sphincterotomy for common bile duct calculi in patients with gallbladders *in situ* considered unfit for surgery. *Gut* 1988; **29**: 114–20.
2. Ingolby CJH, El-Saadi J, Hall RI, Denyer ME. Late results of endoscopic sphincterotomy for bile duct stones in elderly patients with gallbladders *in situ*. *Gut* 1989; **30**: 1129–31.
3. Cotton PB, Vallon AG. Duodenoscopic sphincterotomy for removal of bile duct stones in patients with gallbladders. *Surgery* 1982; **91**: 628–30.
4. Siegel JH, Safrany L, Ben-Zvi JS, Pullano WE, Cooperman A, Stenzel M, Ramsey WHO. Duodenoscopic sphincterotomy in patients with gallbladders *in situ*: report of a series of 1272 patients. *Am J Gastroenterol* 1988; **83**: 1255–8.
5. Martin DF, Tweedle DEF. Endoscopic management of common duct stones without cholecystectomy. *Br J Surg* 1987; **74**: 209–11.
6. Glenn F, Hays DM. The age factor in the mortality of patients undergoing surgery of the biliary tract. *Surg Gynecol Obstet* 1955; **100**: 11–18.
7. Wenckert A, Robertson B. The natural course of gall stone disease. *Gastroenterology* 1966; **50**: 376–81.
8. Dixon JM, Armstrong CP, Duffy SW, Davies GC. Factors affecting morbidity and mortality after surgery for obstructive jaundice: a review of 373 patients. *Gut* 1983; **24**: 845–52.
9. Blamey SL, Fearon KCH, Gilmour WHO, Osborne DH, Carter DC. Prediction of risk in biliary surgery. *Br J Surg* 1983; **70**: 535–8.
10. Hansell DT, Millar MA, Murray WR, Gray GR, Gillespie G. Endoscopic sphincterotomy for bile duct stones in patients with intact gallbladders. *Br J Surg* 1989; **76**: 856–8.
11. Worthley CS, Toouli J. Gallbladder non-filling: an indication for cholecystectomy after endoscopic sphincterotomy. *Br J Surg* 1988; **75**: 796–8.
12. Escourrou J, Cordova JA, Lazarthes F. Early and late complications after endoscopic sphincterotomy for biliary lithiasis with and without their gallbladder *in situ*. *Gut* 1984; **25**: 598–602.
13. Vaira D, Ainley CC, Theis B *et al.* Do patients need cholecystectomy after endoscopic sphincterotomy for bile duct stones? *Gut* 1989; Abstract W78.
14. Tanaka M, Ikeda S, Yoshimoto H, Matsumoto S. The long-term fate of the gallbladder after endoscopic sphincterotomy: complete follow-up study of 122 patients. *Am J Surg* 1987; **154**: 505–9.
15. Gracie WA, Ronsohoff DF. The natural history of silent gall stones: the innocent stone is not a myth. *New Engl J Med* 1982; **307**: 798–800.
16. McSherry CK, Forstenber H, Calhoun F *et al.* The natural history of diagnosed gall stone disease in symptomatic and asymptomatic patients. *Ann Surg* 1985; **202**: 59–63.
17. Rosseland AR, Solhaug JH. Primary endoscopic papillotomy in patients with stones in the common bile duct and gallbladder *in situ*: a 5–8 year follow-up study. *World J Surg* 1988; **12**: 111–15.
18. Hill J, Martin DF, Tweedle DEF. Endoscopic management of common duct stones without cholecystectomy – a five-year follow-up. *Hepato-biliary Surgery* 1990; **2**: A579.
19. Seitzer MH, Sleiger E, Rosato FE. Mortality following cholecystectomy. *Surg Gynecol Obstet* 1970; **130**: 64–6.

20. Doyle PJ, Ward-McQuaid JN, McEwan-Smith A. The value of routine per-operative cholangiography – a report of 4000 cholecystectomies. *Br J Surg* 1982; **69**: 617–19.
21. Solhaug JH, Foskuan O, Rosseland A, Rydberg B. Endoscopic papillotomy in patients with gallbladder *in situ*. *Acta Chir Scand* 1984; **150**: 475–8.
22. Desa LA, Grace PA, Vipond MN, Henderson B, Thompson JN. Gallbladder function after endoscopic sphincterotomy. *Br J Med* 1990; **300**: 1111.
23. Elfstrom J. The timing of cholecystectomy in patients with gallstone pancreatitis. *Acta Chir Scand* 1978; **144**: 487–90.
24. Osborne DH, Imrie CW, Carter DC. Biliary surgery in the same admission for gall stone associated pancreatitis. *Br J Surg* 1981; **68**: 758–61.
25. Ponston GJ, Williamson RCN. Surgical management of acute pancreatitis. *Br J Surg* 1990; **77**: 5–12.
26. Paloyan D, Simonowitz D, Skinner DB. The timing of biliary tract operations in patient with pancreatitis associated gall stones. *Surg Gynecol Obstet* 1975; **141**: 737–9.

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Sheffield cholecystoscope: new instrument for minimally invasive gallbladder surgery

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Symptomatic gallbladder stones should be treated electively, preferably before complications occur[1]. Mortality and morbidity rates increase significantly with emergency operations, especially in the elderly[2]. Recently introduced alternatives to cholecystectomy include extracorporeal shock wave lithotripsy (ESWL) combined with oral dissolution therapy, ultrasound guided gallbladder puncture with stone dissolution or extraction and laparoscopic cholecystectomy.

Selection criteria for ESWL limit its application to about 15 per cent of patients[3]. Ultrasound guided puncture of the gallbladder with tract dilatation and gallstone extraction is a lengthy, complicated procedure requiring radiological guidance. Complications include visceral perforation, bile peritonitis and loss of access[4]. The technique requires general anaesthesia. Contact dissolution with methyl tert-butyl ether, also a complicated procedure, may be associated with duodenal and bile duct damage[5]. Laparoscopic cholecystectomy also requires a general anaesthetic and an extensive pneumoperitoneum. The procedure is under evaluation to define its indications and complications[6].

We report a new instrument which permits gallbladder stones to be removed under direct vision using local or regional anaesthesia by a minimally invasive technique.

Materials and methods

The Sheffield cholecystoscope (patent pending, application no. GB 2 214 428 A) is simple in design (*Figure 1*). Two concentric tubes with an outer diameter of 2·5 cm and an inner diameter of 2 cm are held apart by perforated spacers. The space between the tubes is closed at one end and open at the other. Suction applied to this space has the effect of creating a ring of vacuum which secures the instrument to the fundus of the gallbladder. The instrument is available in 16 cm and 10 cm lengths depending on the distance of the gallbladder fundus from the skin.

A small (2·5 cm), horizontal, muscle splitting incision is made in the right upper quadrant of the abdomen in the anterior axillary line. A 2 cm incision is made in the peritoneum once this is reached. The scope is then inserted into the peritoneal cavity, ensuring a snug fit into the peritoneal incision. An adapted sigmoidoscopic eyepiece is applied to the working end of the scope and a Higginson's syringe is attached to the vacuum channel. A good view of the liver and gallbladder is obtained and any omentum or viscera may be displaced by pumping a small amount of air (in the same way as performing a sigmoidoscopy). However, a formal pneumoperitoneum is not created, avoiding diaphragmatic splinting. Once the fundus of the gallbladder is seen the scope is approximated to it and a vacuum is created. A minimum vacuum of 0·82 mbar for up to 5 min is required for safe fixation to occur and this vacuum is maintained throughout the procedure by continuous suction.

This seal resists distraction of up to 1·2 kg (linear traction). Standard wall suction in most operating theatres is only 0·47 mbar and in practice a Speedivac 2 Vacuum Pump (Edwards High Vacuum, Crawley, UK) has been used.

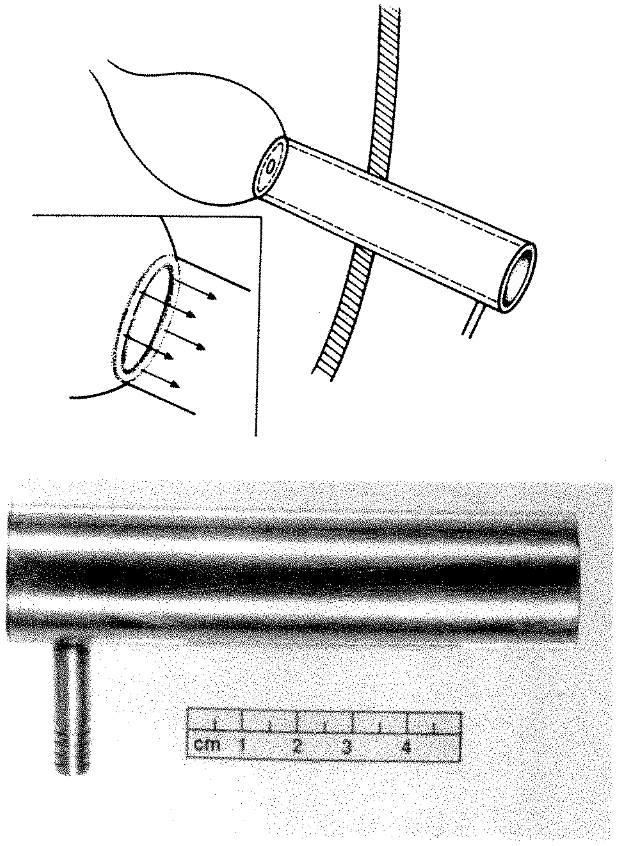

Figure 1 *Method of fixation of the Sheffield cholecystoscope to the gallbladder fundus by vacuum clamping*

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The lumen of the scope is used as the working channel and a 1 cm incision is made in the gallbladder fundus after confirmatory aspiration of bile. A cystoscope or a nephroscope may be inserted and the gallbladder lumen inspected. If necessary large stones may be fragmented mechanically or with contact lithotripsy.

Preliminary pilot studies in 20 cadavers demonstrated the feasibility of the technique before clinical evaluation was carried out.

Results

Precholecystectomy studies

The procedure was evaluated in 19 patients undergoing routine cholecystectomy. Access and gallstone removal was performed without difficulty in 18 patients. One patient proved unsuitable owing to a shrunken, fibrosed gallbladder not detected by preoperative ultrasonography. There was no injury to adjacent viscera in any patient. Histological examination of the suction ring on the gallbladder fundus revealed no detectable damage.

Therapeutic cholecystolithotomy

This was attempted in seven patients who either refused or were unfit for cholecystectomy. The procedure was carried out under local or epidural anaesthesia. Gallstones were safely extracted in six patients. In one patient the omentum was densely adherent to the gallbladder fundus preventing fixation. The time taken for the procedure varied from 35 to 75 min depending on the size and number of gallstones. At the end of the procedure a 20 Fr Foley catheter was left in the gallbladder. All six patients were discharged within 48 h. Cholangiography 10 days later confirmed the absence of residual stones and the catheter was removed. In each case the resulting cholecystocutaneous fistula closed spontaneously. One patient had a minor wound infection treated with antibiotics; there were no other complications.

Discussion

Cholecystectomy by laparoscopic techniques has recently been described[7]. This technique requires general anaesthesia, a large pneumoperitoneum, expensive instrumentation and special skills. Clearly the need for full dissection of the cystic duct and artery will increase the risk of damage to major biliary or vascular structures. The Sheffield cholecystoscope avoids the need for this dissection.

Surgical cholecystostomy with stone removal through a small incision has been described. While this may be possible in cases where the gallbladder is palpable, it would be difficult and hazardous to probe for the gallbladder blindly with a pair of forceps through a 1 inch (2·5 cm) incision. The Sheffield cholecystoscope enables localization and secure fixation of the gallbladder under direct vision.

Radiologically guided gallbladder puncture followed by tract dilatation and gallstone removal is a complicated procedure and often has to be performed in a radiology suite. Complicated anchoring devices have been described to prevent the gallbladder from falling away from the abdominal wall[8]. These anchors may slip out of the gallbladder or may be inextractable[9]. In addition, visceral perforation has been reported as a complication of radiologically guided puncture[4]. The Sheffield cholecystoscope is a surgical instrument which permits gallbladder localization and fixation under vision. This avoids visceral damage and the need for excessive exposure to radiation. The risk of bile leakage is minimized owing to the secure seal between the scope and the gallbladder fundus.

The problem of gallstone recurrence after cholecystolithotomy has led to the investigation of mucosal sclerosants such as ethanol[10] which cause fibrosis and obliteration of the gallbladder, the so called 'chemical cholecystectomy'. Extensive animal studies have confirmed the safety and efficacy of these chemicals[11–13]. One of the potential hazards of this approach is leakage of sclerosant into the peritoneal cavity. This may be prevented by the secure seal between the Sheffield cholecystoscope and the gallbladder facilitating the safe administration of sclerosants.

The Sheffield cholecystoscope permits a cheap, quick and simple method for gallstone removal without the need for a general anaesthetic and leaves only a tiny scar. Further studies are in progress on methods of transluminal cystic duct occlusion and chemical mucosal ablation to prevent the recurrence of gallstones. The instrument is under development by downs Surgical (part of Aesculap Ltd.).

References

1. Finlayson N. Cholecystectomy for gallstones – a good thing if they cause symptoms. *Br Med J* 1989; **298**: 133–4.
2. Glenn F. Silent gallstones. *Ann Surg* 1981; **193**: 251–2.
3. Johnson AG. Extracorporeal shock-wave lithotripsy for gallstones. *J R Soc Med* 1990; **83**: 66.
4. Chiverton SG, Inglis JA, Hudd C, Kellett MJ, Russell RCG, Wickham JEA. Percutaneous cholecystolithotomy: the first 60 patients. *Br Med J* 1990; **300**: 1310–12.
5. Adam G, Knuchel R, Vorwerk D, Gunther RW. Tissue responses of the biliary and digestive system of rabbits after MTBE infusion into the gallbladder. *Invest Radiol* 1990; **25**: 58–61.
6. Cuschieri A, Berci G, McSherry CK. Laparoscopic cholecystectomy. *Am J Surg* 1990; **159**: 273 (Editorial).
7. Dubois F, Icard P, Berthelot G, Levard H. Coelioscopic cholecystectomy. *Ann Surg* 1989; **211**: 60–2.
8. Cope C. Percutaneous subhepatic cholecystostomy with removable anchor. *AJR* 1988; **151**: 1129–32.
9. Cope C, Burke DR, Meranze SG. Percutaneous extraction of gallstones in 20 patients. *Radiology* 1990; **176**: 19–24.
10. Becker CD, Quenville NF, Burhenne HJ. Gallbladder ablation through radiological intervention: an experimental alternative to cholecystectomy. *Radiology* 1989; **171**: 235–40,
11. Getrajdman GI, O'Toole K, Laffey KJ, Martin EC. Cystic duct occlusion and transcatheter sclerosis of the gallbladder in the rabbit. *Invest Radiol* 1986; **21**: 400–3.
12. Salomonowitz E, Frick MP, Simmons RL *et al.* Obliteration of the gallbladder without formal cholecystectomy. *Arch Surg* 1984; **119**: 725–9.
13. Remley KB, Cubberley DA, Watanabe AS, Nelson JA, Colby TV. Systemic absorption of gallbladder sclerosing agents in the rabbit. A preliminary study. *Invest Radiol* 1986; **21**: 396–9.

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Combined surgical and interventional radiological approach for complex benign biliary tract obstruction

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In patients with complicated high benign biliary strictures surgical technique alone cannot exclude the possibility of recurrent problems, and hepatic atrophy/hypertrophy, portal hypertension and intrahepatic stones may all complicate surgical management. A multidisciplinary approach to these complex cases, which minimizes the need for repeated surgical interventions, has been pursued. Roux-en-Y hepaticojejunostomy was performed and an extended limb of the jejunum brought to the abdominal wall to allow access for later radiological intervention. Over a 30-month period 58 biliary–enteric anastomoses for benign disease were performed. Seventeen of these 58 patients were managed using the combined approach. Ten of these 17 patients had complex postcholecystectomy strictures and seven had strictures resulting from inflammatory disease, hepatic resection or congenital problems. A new classification of results of management of bile duct strictures is proposed. Seven patients were classified as 'excellent', six 'good', two 'fair' and two 'poor'. Results were obtained at a mean follow-up of 16 months and it seems likely that in some patients major surgical reinterventions were avoided.

Standard surgical techniques of biliary reconstruction offer a high probability of cure for the majority of patients with intrahepatic or extrahepatic benign biliary stricture[1,2]. Nevertheless, in the most complex cases, intrahepatic stone formation and cholangitis are sometimes unavoidable despite apparently optimal surgical management[2,3]. Similarly, interventional radiological or endoscopic techniques used as primary therapy in this setting have proved disappointing[3-6]; recurrent cholangitis associated with tube blockage or dislocation of the endoprosthesis occurs often following successful decompression, and the procedures themselves may be technically impossible owing to problems of access.

A multidisciplinary approach to the diagnosis and management of the very complex cases of benign biliary obstruction has been followed in the Department of Visceral and Transplantation Surgery at Inselspital, Berne to combine the advantages of interventional radiology and surgery. A regular conference between surgeons, radiologists and gastroenterologists proved essential and allowed a review of the clinical situation as well as the radiological and endoscopic data, so that operative strategy could be planned in advance.

The surgical goal consisted not only of an attempt at definitive repair but, importantly, a preoperative decision to establish permanent radiological access to spare the patient repeated surgery in the event of recurrent stricture or intrahepatic stone formation. The patients chosen for this approach were those in whom it seemed likely that neither surgical, radiological nor endoscopic techniques alone could offer hope for a long-term clinical success. In practical terms, this meant that the approach was chosen where three or more of the known risk factors were involved (*Table 1*). This report details the results obtained in 17 patients managed by this method.

Patients and methods

Over a 30-month period 58 biliary–enteric anastomoses for benign biliary disease were performed. Seventeen of these 58 patients (ten women, seven men; mean age 55 years (range 25–75 years)) suffering from benign biliary strictures were selected for management with the combined surgical–radiological approach.

Aetiology

There were ten patients with postcholecystectomy strictures and two with obstruction secondary to alveolar or cystic echinococcosis. One stricture occurred after previous hepatic resection and one followed multiple previous operations, the first of which had been done in childhood for supposed partial congenital biliary atresia. There was one instance of recurrent pyogenic cholangitis, one patient had obstruction related to a complicated choledochal cyst. A further patient had diffuse inflammatory strictures following multiple previous operations for complications of portal vein thrombosis and cholecystectomy. The level of benign strictures was classified according to Bismuth[1] (*Figure 1*). However, some patients showed segmental, lobar, or diffuse obstruction and strictures, forming a separate group which does not lend itself to the Bismuth classification.

Clinical presentation and risk factors

All patients presented with right upper abdominal discomfort or pain, and all suffered from recurrent intermittent jaundice and fever from cholangitis. The mean number of previous hepatobiliary operations was 2·6 (range 0–5 operations); a total of 44 procedures had been performed on 15 of the patients and in only two patients was there no previous surgery. Twenty-nine previous attempts at stricture repair had

Table 1 *Risk factors: patients with three or more risk factors were considered for treatment by a combined approach*

High biliary tract obstruction (types 3, 4 and 5)
Segmental or diffuse biliary stricture
Hepatic atrophy/hypertrophy complex
Multiple previous operations
Portal hypertension
Intrahepatic concretions or debris
Recurrent cholangitis and jaundice
Impaired liver function, fibrosis/cirrhosis
External and/or internal biliary fistulae

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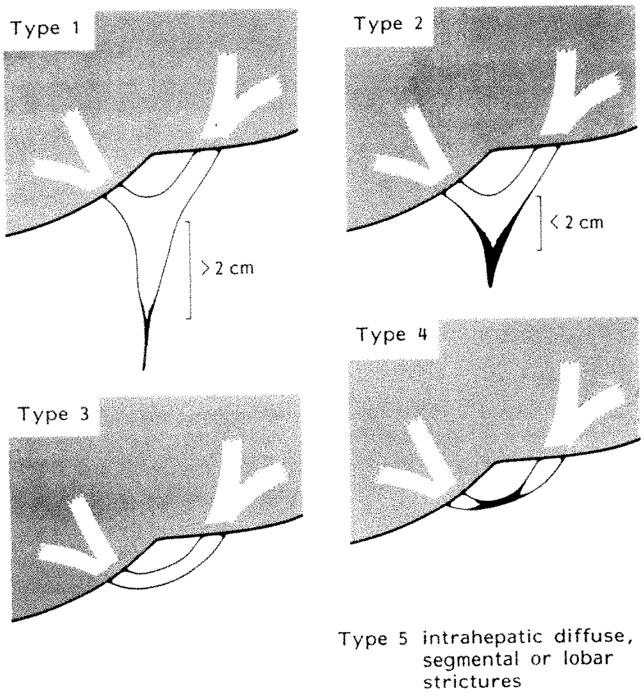


Figure 1 *Classification of bile duct strictures (types 1–4, after Bismuth[1])*

been performed in 13, all at other institutions. There were two type 2, four type 3 and three type 4 strictures. Six patients showed a predominantly segmental pattern of stricture and two had diffuse type 5 strictures. Eight patients had intrahepatic concretions, one associated with a foreign body (the residual tube placed at a previous operation); two patients had debris or cystic material in the intrahepatic bile ducts. Seven patients had no demonstrable stones or debris in the bile ducts. Seven patients presented with biliary fistulae (three external, two internal, two combined internal and external). Portal hypertension evidenced by oesophageal varices, splenomegaly and/or intraoperative-proven venous collaterals was documented in ten patients. In 11 patients a significant lobar and/or segmental hypertrophy/atrophy-complex[1] of the liver could be demonstrated. Four displayed hypertrophy of the right lobe and two hypertrophy of the left lobe and in seven patients impaired liver function was proven by hepatoiodida scintigraphy, aminopyrine breath test and/or galactose elimination capacity. Eight patients showed variable degrees of histologically-proven liver fibrosis/cirrhosis[1]. With specific regard to the nine risk factors in *Table 1*, five patients presented with three, one patient with four, three patients with five, three patients with six and five patients with seven risk factors, which illustrates the severity of disease in patients selected for this combined approach.

Diagnostic approach

Ultrasound (76 per cent), computed tomography (CT) (59 per cent) and hepatoiodida scan (59 per cent) were generally the first procedures performed and suggested the site of the obstruction, the presence or absence of dilated ducts, and of lobar or segmental hypertrophy and/or atrophy of the liver. For precise localization of the obstruction, percutaneous transhepatic cholangiography (PTC; 41 per cent), fistulogram (18 per cent) or endoscopic retrograde cholangiopancreatography (ERCP; 35 per cent) were performed in 16 of 17 patients, depending on the level of obstruction or presence of external fistula (in one patient sufficient information was available from barium meal alone). Hepatoiodida scan demonstrating segmental obstruction and a barium meal showing direct peristalsis of contrast material into the biliary tree from an improperly constructed jejunal loop were the most important studies in two cases. Angiography with late phase portography (four patients), duplex ultrasonography (five patients) and barium meal examination (three patients) were helpful in the recognition of anatomical or functional changes involving the major hepatic vessels, or the presence of reflux through previous Roux-en-Y loops. Generally, multiple examinations tailored to the individual patient were necessary to arrive at an exact aetiological, functional and anatomical diagnosis enabling a well-informed decision concerning management. The strategy was then discussed by a multidisciplinary team of surgeons, radiologists and gastroenterologists.

Operative management

After suitable preoperative preparation (including nutritional support and correction of electrolyte and metabolic disturbances), laparotomy was performed under antibiotic cover (piperacillin 4 g three times daily). Biliary enteric anastomosis with a 70 cm Roux-en-Y retrocolic jejunal loop was the preferred procedure. The difficult anatomical situation of some lesions prevented an anastomosis above the stricture and the construction of an accurate ideal mucosa to mucosa anastomosis. Complete intraoperative clearance of intrahepatic stones or debris was also often not possible or deliberately avoided. If direct access to the stricture was not feasible at the time of operation because of dense adhesions, portal hypertension or intrahepatic localization of the stricture (type 5), the Roux-en-Y loop was anastomosed to distal bile ducts and the stricture was left for a later radiological approach. A single layer anastomosis was performed according to the technique of Blumgart and Kelley[1,7] and an extended limb of the Roux-en-Y loop was subsequently fixed[8] at a convenient point to the abdominal wall (*Figure 2*). Other reports[9–13] describing this approach have included some advocates of formal stoma formation of the Roux-en-Y loop to create access for radiological intervention. It is important to emphasize that in this series the loop was merely secured to the anterior abdominal wall and a silicon tube was passed transcutaneously into the loop to lie with its free end either within the biliary tree across the anastomosis or simply within the jejunum below the anastomosis.

Results

Operative results

Choledochojejunostomy was performed in two patients, and hepaticojejunostomy in 12 (four as shown in (1) and ten as

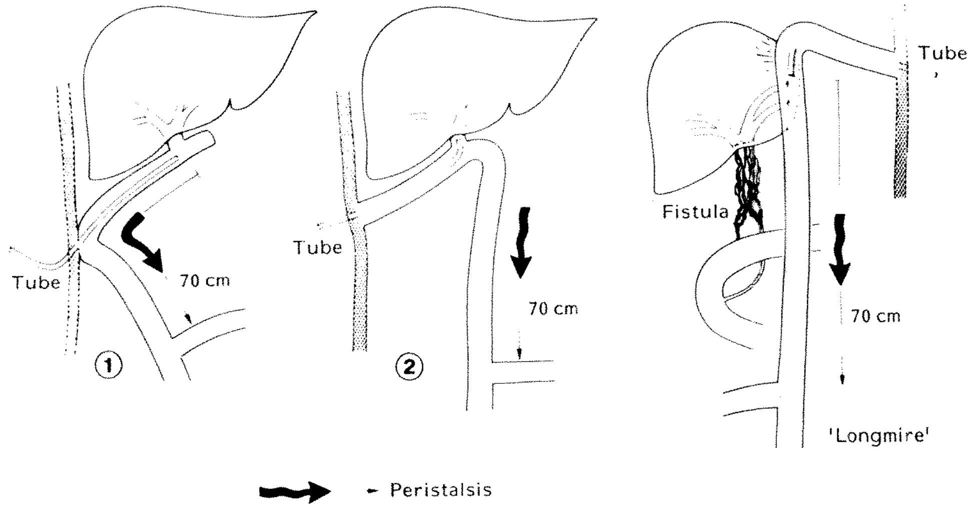


Figure 2 *Variations of the Roux-en-Y reconstruction allowing access for radiological intervention*

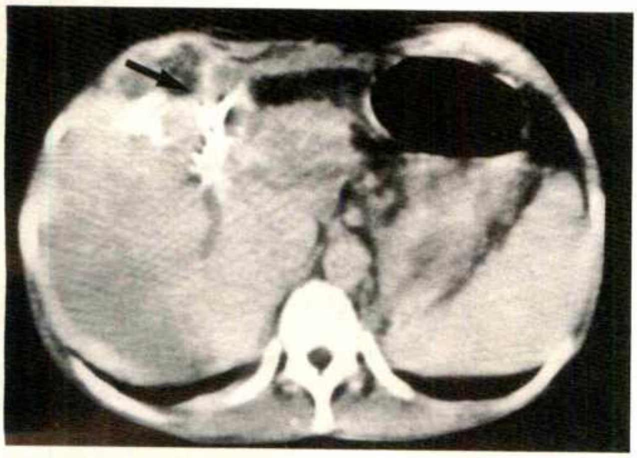


Figure 3 *Computed tomographic scan showing hilus (arrow) of liver at the anterior abdominal wall in a patient with* Echinococcus alveolaris *and liver distortion consequent on rotation by atrophy–hypertrophy complex*

shown in (2) in *Figure 2*). An approach to the segment III duct in the umbilical fissure was used in one case and a modified Longmire procedure (*Figure 2*) in two further patients[7]. The 12 hepaticojejunostomies included direct approaches to the hilus (or anastomosis to a common orifice of the right and left duct sewn together) or multiple duct anastomosis to individual segmental ducts exposed in the region of the porta hepatis. A silicon tube was placed in 12 patients in the intrahepatic biliary ducts and in five patients, lying within the jejunum adjacent to the anastomosis.

Bacterial culture showed single organisms in six patients, multiple organisms in five and no growth in six. *Escherichia coli* was the most frequent contaminant with *Enterococcus* being encountered twice.

There was one serious intraoperative complication consisting of an injury to the portal vein (in the patient with *Echinococcus alveolaris* and hepatic resection 17 years previously). In this patient hypertrophy of the residual liver had lead to a remarkable anteromedial rotation and displacement of the hilus with the portal structures lying directly beneath a thin abdominal wall (*Figure 3*). The portal vein injury was immediately repaired.

Postoperative bile collections required drainage in three patients and three postoperative biliary fistulae closed spontaneously within 24 days.

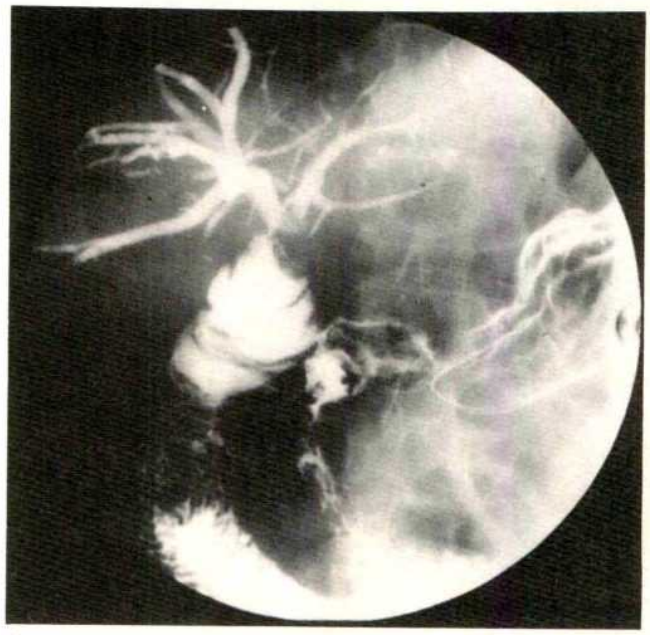
There was no 30-day mortality. One patient died of hepatic insufficiency because of infected ascites 4 months after surgery (although before this she had been steadily improving at home).

Radiological results

Postoperative tubography was carried out in all patients under antibiotic cover (piperacillin 4 g, one dose). In three cases small calculi or debris and cystic material could be washed out (utilizing six irrigation procedures) through the trans-anastomotic silicon tube. In six patients nine procedures were required to dilate the anastomosis using a 7 Fr balloon catheter (diameter 10 mm, length 4 cm; Gaurbet, France) (*Figure 4*). All dilatations were performed in patients in whom access to the site of stricture was not possible during operation, either because of intrahepatic location (four cases) or dense adhesions from previous operations and/or portal hypertension (two cases). The classification of these strictures included one grade 2 and one grade 4 stricture and four lobar and/or segmental strictures (grade 5). In three patients eight extraction procedures of residual intrahepatic calculi were performed (Dormia basket, Cook) (*Figure 5*). After completion of the necessary interventional radiological procedures and the in-hospital contrast tubogram examinations, the drain was withdrawn into the Roux-en-Y loop so that the distal end lay in close proximity to, but not stenting, the anastomosis. After satisfactory clinical follow-up, laboratory tests and contrast imaging of the anastomosis 3 months after operation (usually combined with hepatoiodida scans as in *Figure 6*), drains were removed. The patients were assessed at intervals of 6 months and hepatoiodida scans were repeated yearly (*Figure 6*). In the event of recurrent stricture formation after removal of the drain, the Roux-en-Y loop was punctured under ultrasound guidance (one patient). Attempting a similar procedure in a further patient failed and a small incision under local anaesthetic was made to find the loop for reintubation. Only one late surgical reintervention was necessary (at 8 months in the patient with alveolar echinococcosis) to drain a late intrahepatic abscess. There were no technical difficulties and no complications from the interventional radiological procedures.

Follow-up

Results were classified as shown in *Table 2*. Six of the patients have been followed for at least 2 years and have had in three



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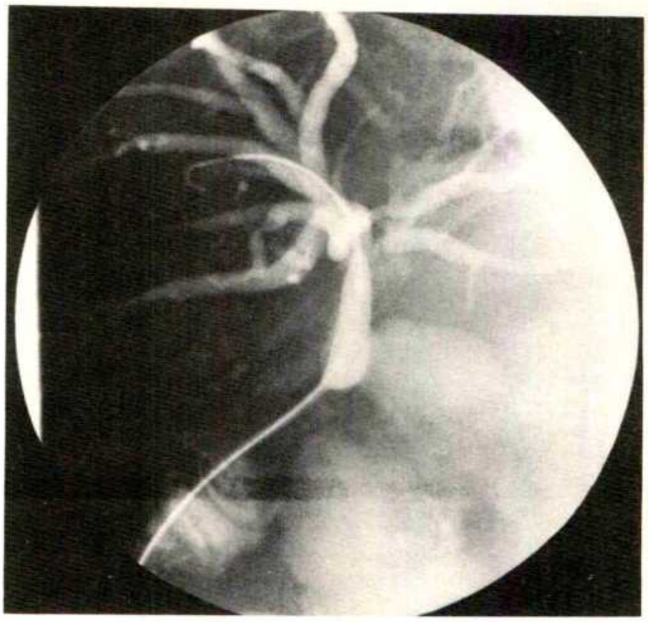
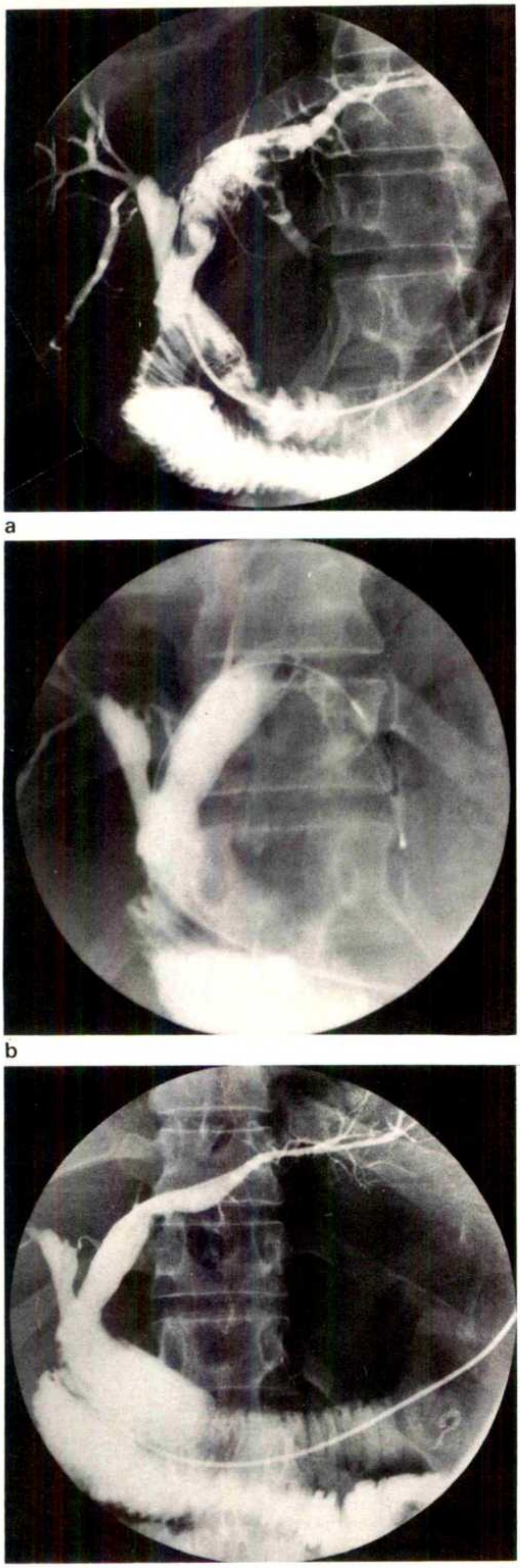


b

Figure 4 **a** *Biliary stricture at the site of anastomosis.* **b** *Dilatation of stricture by radiological balloon dilatation through Roux-en-Y limb*



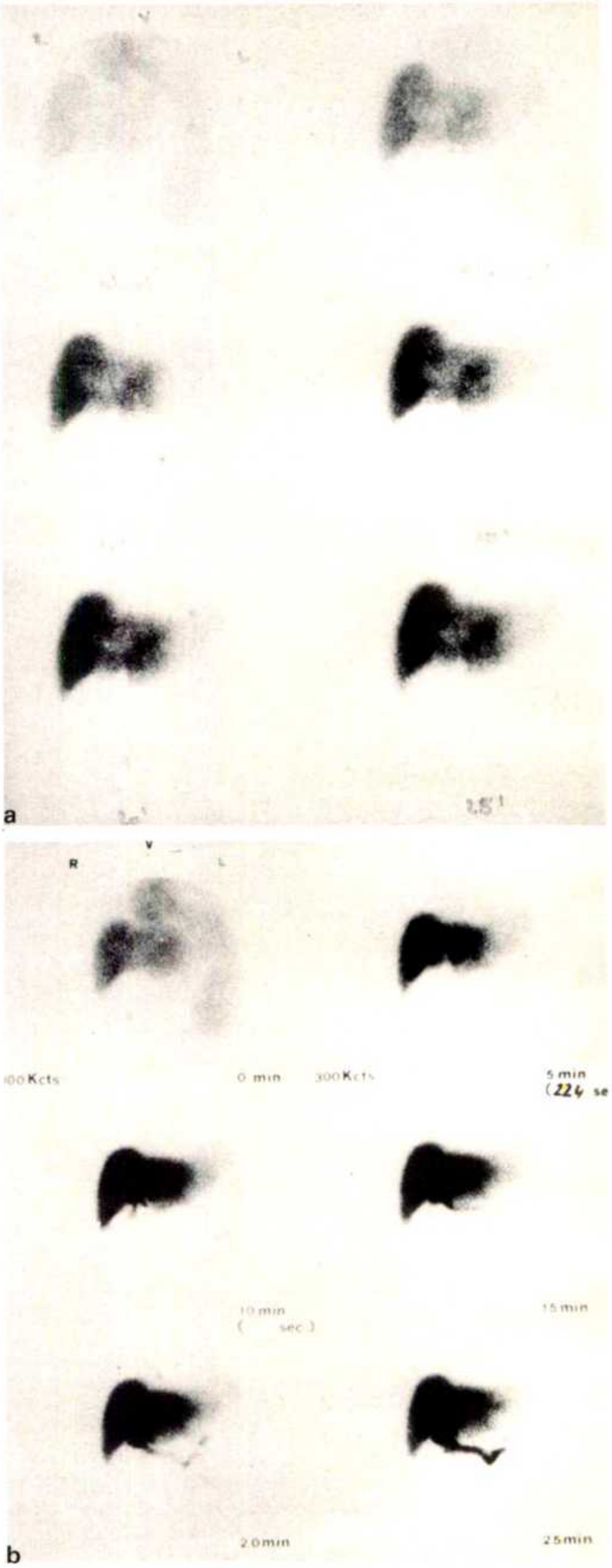


Figure 6 **a** *Preoperative hepatoiodida scintigraphy with slow heterogenous uptake and almost no excretion until 25 min.* **b** *Faster and more homogeneous uptake with excretion into the gut at 10 min; 1 year after operation*

Figure 5 **a** *Postoperative tubogram in a patient with intrahepatic stones electively left in the intrahepatic bile ducts at operation for subsequent radiological extraction.* **b** *Removal of stone in the segment III duct with Dormia basket.* **c** *Stone-free biliary tract after radiological intervention (segment III duct not demonstrated on this radiograph)*

Table 2 *Classification of results*

Classification	Symptoms (cholangitis)	Laboratory alkaline phosphatase	Radiology
Excellent	None	Normal	No obstruction or calculi
Good	None	Elevated	No obstruction or calculi
Fair	Improved	Elevated	Obstruction and/or calculi
Poor	Persistent or worse	Elevated	Obstruction and/or calculi

cases an 'excellent' and in one case a 'good' result. One patient had a 'fair' and one a 'poor' result. In this latter patient technical limitation imposed by extensive adhesions and portal hypertension prevented access to the hilus and adequate resection of the underlying disease (*E. alveolaris*).

Of the five patients followed for at least 1 year, three showed 'excellent' and two 'good' results and of the six most recently treated patients (3–9 month follow-up) there is one 'excellent', three 'good', one 'fair' and one 'poor' result. This last patient died 4 months after operation from infected ascites and sepsis.

Overall, there were seven 'excellent', six 'good', two 'fair' and two 'poor' results at a mean follow-up of 16 months.

Discussion

Successful surgical therapy is possible in a large proportion of patients with biliary tract strictures[1,2]. In selected cases stricture dilatation may be performed with satisfactory results[3,5,6,11,14–16]. However, for complex cases of high biliary stricture optimal management must not only offer the possibility of definitive surgical repair, but also anticipate possible recurrence, to prevent the need for further surgical intervention[1,9,10,12]. Thorough preoperative assessment with multidisciplinary discussion of individual patients is a prerequisite for successful therapy.

Although ultrasound and/or computed tomography provide valuable information regarding the level of obstruction (dilatation of the intrahepatic biliary tree and especially distortions of liver anatomy from atrophy/hypertrophy of hepatic lobes or segments), direct cholangiography (PTC or ERCP) offers the best means for the precise localization of the obstruction and definition of the anatomy of the biliary tree. Hepatoiodida scan is particularly useful to assess the qualitative function of the liver and may also reveal lobar or segmental retention of tracer or evidence of hypertrophy/atrophy of the liver. Duplex ultrasonography and angiography provide important information concerning patency of lobar branches of the portal vein and hepatic artery.

As a consequence of clinical and radiological evaluation high risk patients presenting with complicated problems can be assigned to the combined approach. As described, we have used a biliary enteric anastomosis with a 70 cm Roux-en-Y loop with an extended loop fixed at a convenient point to the abdominal wall[8]. If possible, we try to ensure there is access to the stricture for intraoperative dilatation or removal of stones. A direct anastomosis to the bile ducts proximal to the stricture was not possible in the cases described here. The extended limb is preferably brought through the abdominal wall and fixed subcutaneously, where it may be easily palpated and punctured radiologically. In patients in whom the loop was fixed to the abdominal wall internally, radiological access was more difficult and in one patient the end of the limb had to be found surgically. The disadvantages of formal stoma formation as described by some authors[9,10,12] are patient discomfort from possible reflux of mucus or bile[10] and contamination as a result of the externally open gut communicating with the bile ducts. The extent to which radiology is facilitated seems similar for both techniques when the present series is compared with others[9,10,12].

Finally, it is interesting to note that many of the strictures examined in this series could not be classified by the Bismuth method (*Figure 1*) and it seems reasonable to suggest a modification of the classification which includes intrahepatic or segmental strictures (either alone or combined with extrahepatic strictures) as a fifth category. Furthermore, the classification of results in terms of stricture site and patency alone is inadequate, and in this series the symptomatic, biochemical and radiological assessment allowed a more critical evaluation. Although the period of postoperative and postinterventional observation has been limited, we have been able to demonstrate a substantial improvement in the clinical and laboratory status of our patients. While comparison of results of the management of bile duct strictures in various series is always difficult we would suggest that the classification of results used in this study might be adopted for further reports regarding the management of benign biliary strictures.

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References

1. Blumgart LH. Benign biliary stricture. In: Blumgart LH, ed. *Surgery of the Liver and Biliary Tract*. Edinburgh: Churchill Livingstone, 1988: 721–52.
2. Warren KW, Jefferson MF. Prevention and repair of strictures of the extrahepatic bile ducts. *Surg Clin North Am* 1973; **53**: 1169–90.
3. Lundquist A. Interventional radiological techniques in the liver and biliary tract. In: Blumgart LH, ed. *Surgery of the Liver and Biliary Tract*. Edinburgh: Churchill Livingstone, 1988: 473–90.
4. Mendez G, Russel E, LePage JR, Guerra JJ, Posniak RA, Trefler M. Abandonment of endoprosthetic drainage technique in malignant biliary obstruction. *AJR* 1984; **143**: 617–22.
5. Mueller PR, Ferucci J, Teplick SK *et al.* Biliary stent endoprosthesis: analysis of complications in 113 patients. *Radiology* 1985; **156**: 637–9.
6. Mueller PR, Van Sonnenberg E, Ferrucci JT. Percutaneous biliary drainage: technical and catheter-related problems in 200 procedures. *AJR* 1982; **138**: 17–23.
7. Blumgart LH. Hilar and intrahepatic biliary-enteric anastomosis. In: Blumgart LH, ed. *Surgery of the Liver and Biliary Tract*. Edinburgh: Churchill Livingstone, 1988: 899–913.
8. Schweizer W, Baer HU, Nudelmann LI *et al.* A combined surgical and interventional radiological approach in biliary obstruction. *Helv Chir Acta* 1988; **55**: 583–91.
9. Gibson RN, Adam A, Czerniak A *et al.* Benign biliary strictures: a proposed combined surgical and radiological management. *Aust NZ J Surg* 1987; **57**: 361–8.
10. Barker EM, Winkler M. Permanent-access hepaticojejunostomy. *Br J Surg* 1984; **71**: 188–91.
11. Carrasco CH, Wallace S, Charnsangavej C *et al.* Expandable biliary endoprosthesis: an experimental study. *AJR* 1985; **145**: 1279–81.
12. Russel E, Hutson DG, Guerra JJ, Nunez D, Yrizarry JM, Schiff E. Dilatation of biliary strictures through a stomatized jejunal limb. *Acta Radiol Diag* 1985; **26**: 283–7.
13. Russel E, Yrizarry JM, Huber JS *et al.* Percutaneous transjejunal biliary dilatation: alternate management for benign strictures. *Radiology* 1986; **159**: 209–14.
14. Chen MF, Yan YY, Lee TY. Percutaneous transhepatic cholangioscopy. *Br J Surg* 1987; **74**: 728–30.
15. Martin EC, Fankuchen EI, Schultz RW, Casarella WJ. Percutaneous dilatation in primary sclerosing cholangitis: two experiences. *AJR* 1981; **137**: 603–5.
16. Martin EC, Karlson KB, Fankuchen EI, Mattern RF, Casarella WJ. Percutaneous transhepatic dilatation of intrahepatic biliary strictures. *AJR* 1980; **135**: 837–40.

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Primary sclerosing cholangitis: surgical options, prognostic variables and outcome

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The natural history of primary sclerosing cholangitis (PSC) is poorly defined and its management remains controversial. Forty-eight symptomatic patients (median age 39 years, range 8–67 years; 30 male) with PSC were reviewed retrospectively. Thirty patients had inflammatory bowel disease. Four patients (8 per cent) developed or had an associated malignancy. Twenty-one (44 per cent) died; overall 5 year actuarial survival was 30 per cent. Twenty-three patients had 27 non-transplant related biliary operations (16 patients specifically for PSC) of whom 12 died. Serum bilirubin was the only parameter to improve after biliary surgery. Seventeen patients (35 per cent) underwent orthotopic liver transplanation (OLT) of whom nine are currently alive (1 year projected survival of 55 per cent). Previous biliary surgery correlated with a poor outcome ($P<0.0001$) *after OLT. Being male, presence of cirrhosis, duration of symptomatic disease (>3 years) and a serum bilirubin level > 100 µmol/l at presentation, were independently associated with a poor outcome* ($P<0.05$). *These data provide evidence that PSC is a progressive disease and conventional surgical options have little influence on the outcome. Previous biliary surgery adversely affects outcome following OLT. For progressive liver disease, liver transplantation should be considered the treatment of choice.*

Primary sclerosing cholangitis (PSC) is an idiopathic disease characterized by chronic inflammation and obliterative fibrosis affecting the intra- and extrahepatic biliary tree[1]. The disease generally follows an episodic but progressive course leading to cirrhosis, portal hypertension and liver failure.

PSC was first described by Delbet in 1924[2] and was, until recently, considered a rare disease. A variety of treatment regimens including anti-inflammatory and immunosuppressive drugs[3], steroids[4], colchicine[5], D-penicillamine[6], cholestyramine[7] and nasobiliary lavage[8] have been advocated. As the natural history is poorly defined, medical management has largely been empirical and of no proven benefit.

Some centres advocate an aggressive surgical approach of stricture excision, hepaticoenteric or choledochoenteric anastomosis with or without transanastomotic stenting[9–12]. More recently, an increasing number of patients are being considered for liver replacement[13]. This article reviews our experience in the management of patients with PSC evaluating the outcome of differing surgical options and determining prognostic variables.

Patients and methods

Between 1 January 1984 and 28 February 1989, 48 patients with PSC were admitted to The Liver Unit, Queen Elizabeth Hospital, Birmingham. The diagnosis was established by: typical cholangiographic findings of multifocal strictures, beading and irregularity of the biliary tree, compatible histological features on liver biopsy, and the absence of other features causing secondary biliary cirrhosis.

Signs and symptoms attributed to PSC included malaise, jaundice, pruritis, abdominal pain, weight loss, fever, ascites, hepatic encephalopathy and variceal bleeding. Patients were classified as asymptomatic if no symptoms could be linked to their liver disease at diagnosis which was usually detected by abnormal biochemistry. Follow-up data regarding outcome was available on all patients to April 1989.

To compare differences between groups of patients χ^2 analysis was performed. Analysis of survival was performed using the Kaplan–Meier method. Univariate and multivariate analysis (Cox's survival analysis with correlates) was performed to ascertain the variables producing significant differences in survival (end-point being death or transplantation) using the BMDP 1L and 2L software programs (BMDP Statistical Software, Inc., Los Angeles, California, USA) on a mainframe computer.

Results

Clinical features

Forty-eight patients (median age 39 years, range 8–67 years, 30 male, 18 female) were referred (*Table 1*). Thirty-eight patients (79 per cent) were tertiary referrals of whom 28 were from outside the West Midlands. Common presenting features were jaundice (64 per cent), cholangitis (54 per cent), encephalopathy (25 per cent) and variceal haemorrhage (21 per cent). Liver biochemistry was abnormal in the majority of patients; raised alkaline phosphatase in 96 per cent (median 1173 units/l, range 47–5403 units/l; normal range 70–290 units/l), raised aspartate transaminase in 98 per cent (median 131 units/l, range 26–1120 units/l; normal range 5–20 units/l) and raised bilirubin in 91 per cent (median 102 µmol/l, range 6–857 µmol/l; normal range 5–20). Histology was available from 45 patients: 23

Table 1 *Primary sclerosing cholangitis: patient characteristics*

Variable	All patients ($n=48$)	Percentage (%)
Age at diagnosis	39 (8–67)*	
Sex (male:female)	30:18	62:38
Ulcerative colitis	28	58
Crohn's disease	2	4
Hepatobiliary tumour	4	8
Number transplanted	17	35
Follow-up: diagnosis (months)	77 (16–339)*	
Follow-up: referral (months)	20·5 (4–145)*	
Deaths	21	44

* Values are median (range)

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Table 2 *Primary sclerosing cholangitis: symptom status and disease progression*

Symptom status	At diagnosis ($n=48$)*	At presentation ($n=48$)†	At last follow-up ($n=27$)‡
Asymptomatic	16 (33)	4 (8)	9§
Symptomatic	32 (67)	44 (92)	18 (100)¶

Values in parentheses are percentages. * All patients at time of diagnosis; † all patients at presentation to our unit; ‡ 21 patients died during follow-up; § 9 patients alive following orthotopic liver transplantation and free of recurrence of primary sclerosing cholangitis; ¶ 18 non-transplanted patients alive at last follow-up (all symptomatic for primary sclerosing cholangitis)

Table 3 *Primary sclerosing cholangitis: biliary operations*

Operation	Number of patients
Cholecystectomy	4
Cholecystectomy and exploration CBD	2
Cholecystectomy and sphincteroplasty	1
T tube/stent drainage	5
Choledochoduodenostomy	1
Choledochojejunostomy and Roux-en-Y	4
Hepaticojejunostomy	6

27 operations in 23 patients. CBD, common bile duct

(51 per cent) had established cirrhosis and the remainder had findings consistent with PSC.

Twenty-eight patients (58 per cent) had associated ulcerative colitis (UC), the diagnosis being made before the onset of PSC in 22 patients, at a mean of 10·4 years (range 1–23 years). In six patients PSC clearly preceded the clinical diagnosis of UC. At the time of referral the bowel disease was in remission in seven patients and of mild to moderate severity in the remainder. Sixteen patients (57 per cent) were on Salazopyrin® (Pharmacia Ltd, Milton Keynes, UK) and three had had bowel surgery. There was no statistically significant difference in demographic features, presentation, treatment or outcome between patients with or without inflammatory bowel disease (data not shown).

Four patients (8 per cent) developed or had associated hepatobiliary malignancy. One patient (orthotopic liver transplant (OLT) number 119) had hepatocellular carcinoma and severe dysplasia as an incidental finding in the liver removed at transplantation. The remaining three patients had cholangiocellular carcinoma. It was found in posttransplant histology in one patient (OLT 139, male, age 40 years), as metastatic disease at laparotomy before liver grafting (not performed) in another (female, age 52 years) and in follow-up for PSC in another patient (male, 35 years).

The dominant site(s) of disease was located in the common bile duct in 31 patients (72 per cent), the bifurcation of the common hepatic duct in 20 patients (42 per cent) and the intrahepatic bile ducts in 28 patients (58 per cent).

In an attempt to assess progression patients were classified according to symptoms (*Table 2*). At initial diagnosis of PSC 16 patients (33 per cent) were asymptomatic, but at presentation to the Queen Elizabeth Hospital only four were asymptomatic and at last follow up (April 1989), all patients (excluding those transplanted) were symptomatic.

Endoscopic retrograde cholangiopancreatography (ERCP) dilation

Thirteen patients (27 per cent) had ERCP dilation of a biliary stricture (two patients had nasobiliary drainage) complicated by ascending cholangitis in four, haemobilia (one requiring surgery) in two and one patient had extravasation of contrast from the common bile duct. ERCP produced clinical or biochemical improvement in five patients (39 per cent).

Biliary surgery

Twenty-seven non-transplant related biliary operations were performed in 23 patients (*Table 3*). Only eight operations in seven patients were performed in the Queen Elizabeth Hospital. Seven patients had surgery for cholelithiasis and 16 surgery specifically for PSC (progressive jaundice was the main indication in 13 patients, recurrent cholangitis in two, and abdominal pain in one patient).

The bifurcation of the common hepatic duct was the dominant site of disease in seven patients (44 per cent) and the common bile duct in the remainder. Seven of these patients died; three following liver replacement, two due to post-operative problems (one multi-organ failure; one bleeding) and two due to malignancy (one cholangiocarcinoma; one lung cancer). Only two patients (12·5 per cent) had clinical and bichemical improvement after biliary surgery. A further two patients had initial improvement but one developed recurrent cholangitis and the other had increasing jaundice. Biliary surgery resulted in improvement in the bilirubin level only (preoperative median 201 μmol/l, range 10–435 μmol/l; post-operative median 127 μmol/l (range 14–527 μmol/l, $P<0{\cdot}05$).

Liver transplantation

Thirty-nine patients were assessed for transplantation; 23 were placed on the 'active' list, 16 were excluded because they were too ill, too early or refused transplantation and six died waiting for a donor liver.

Nineteen grafts were performed in 17 patients with hepatobiliary disease due to PSC. Seven of the eight transplanted patients who had undergone previous biliary surgery died (*Figure 1*) compared with only one of the nine patients who had not undergone biliary surgery. Death was due to perioperative bleeding (three), graft infarction (one, incidental hepatocellular carcinoma), multi-organ failure (one), inferior vena cava thrombosis/acute renal failure (one), metastatic cholangiocellular carcinoma (one) and septicaemia (one).

Both patients who required re-transplanation died; OLT 72/73 (previous biliary surgery) died of perioperative bleeding, and OLT 95/212 due to sepsis at 2 months following the second graft (19 months after first graft).

Survival

From referral, the median actuarial survival was 9·8 months with 30 per cent surviving 5 years (*Figure 2*).

Univariate analysis. Univariate analysis of clinical factors associated with a poor outcome was performed using referral to our unit as the starting point and death or transplantation (with censoring) as the end point. Males ($P=0{\cdot}04$), cirrhotics ($P<0{\cdot}003$), duration of disease greater than 3 years ($P=0{\cdot}0008$) and a serum bilirubin level >100 μmol/l ($P=0{\cdot}0024$) at referral correlated with a worse outcome. Age and presence or absence of symptoms or ulcerative colitis were not significant.

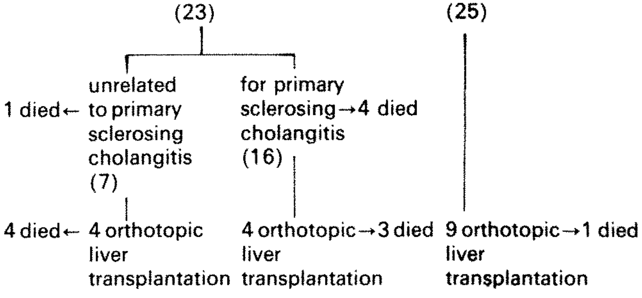
Primary sclerosing cholangitis
Biliary surgery (23)
No surgery→8 died (25)
1 died←
unrelated to primary sclerosing cholangitis (7)
for primary sclerosing cholangitis (16)
→4 died
4 died←
4 orthotopic liver transplantation
4 orthotopic liver transplantation
→3 died
9 orthotopic liver transplantation
→1 died

Figure 1 *Previous biliary surgery and outcome*

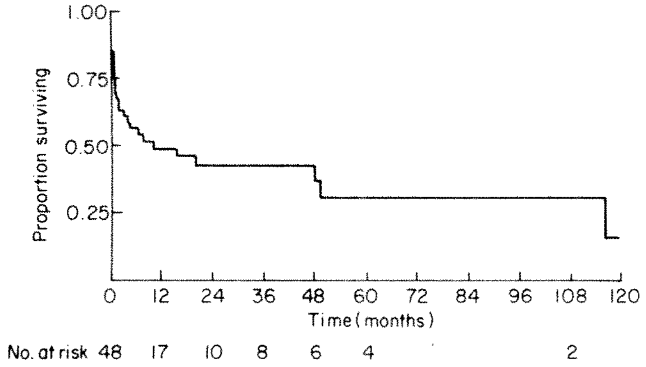

Figure 2 *Life-table analysis of survival of patients* (n = 48) *with primary sclerosing cholangitis from referral by the Kaplan–Meier method*

Extrahepatic disease was associated with a good outcome, either as the sole site ($P=0{\cdot}012$) or in association with other sites ($P=0{\cdot}03$). Seventeen patients (35 per cent) had OLT of whom nine are alive. The one year actuarial survival following OLT was 55 per cent (median 21 months) and previous biliary surgery was the only variable correlating with a poor outcome ($P<0{\cdot}0001$).

Analysis of variance (*Mann–Whitney* U *test*). Duration of disease correlated with sex (male $P<0{\cdot}023$), cirrhosis ($P<0{\cdot}005$) and biliary surgery ($P<0{\cdot}01$). Serum bilirubin at referral was significantly lower in patients with extrahepatic PSC ($P<0{\cdot}05$). The serum bilirubin level strongly correlated with outcome. The most clinically useful value appeared to be 4 × normal (100 μmol/l) which was also the median value in our series. Outcome was worse when serum bilirubin was >100 μmol/l ($P=0{\cdot}0025$).

Multivariate analysis. Cox's multivariate regression analysis was performed to determine if independent variables gave rise to significant differences in survival. Using the step-wise proportional hazards model, log transformation of bilirubin was the most significant variable (χ^2 of model $=11{\cdot}9$, 1 degree of freedom (d.f.); $P=0{\cdot}0006$). The addition of a further variable, duration of disease, gave only a marginal improvement ($P=0{\cdot}068$) in the model ($\chi^2=15{\cdot}7$, 2 d.f.; $P=0{\cdot}004$) but the predictive power of this model was limited as only 8 per cent of the variations in the data were represented ($R^2=0{\cdot}08$).

Discussion

Traditional surgical management included choledochotomy and prolonged T tube and hepaticoenteric or choledochoenteric anastomosis[9,12]. Silastic® (Dow Corning, Reading, UK) transhepatic biliary stents have been used following resection to support the choledochoenteric anastomosis[10,11]. A major problem of assessing the efficacy of different treatment options is that criteria for estimation of severity of disease is arbitrary and the grading subjective.

This data confirms that PSC is a progressive and unrelenting condition in which one-third of patients are asymptomatic at diagnosis. All patients become symptomatic in a relatively short interval. This is in accordance with the Mount Sinai[14] and the Mayo Clinic[15,16] experiences. The Mayo group[16] in a controlled prospective trial of 70 patients with PSC found 80 per cent had clinical or histological progression during a 3-year follow-up period. The epidemiological features of the patients in this series are similar to those previously reported, acknowledging that the full spectrum of PSC is not seen. From referral the median actuarial survival was only 9·8 months whereas from diagnosis it was 10 years. Most other centres have reported a similar bias including patients at a late stage in the disease[13,14,16].

Reconstructive biliary surgery does not appear to alter the progression or natural history of PSC. The high incidence of complications (for example, cholangitis), the lack of long-term efficacy and increased risk to the patient of subsequent liver transplantation would question the role of aggressive surgical management. When surgery is limited to localized disease at the bifurcation or extrahepatic biliary tree good results have been obtained in uncontrolled series in cirrhotic patients[11,17].

The Johns Hopkins group[11] have shown good results can be achieved in the non-cirrhotic with localized disease but as the disease is progressive, many will ultimately require transplantation.

The Pittsburgh group[15] demonstrated that liver transplantation is the most effective therapy for end-stage liver disease due to PSC with 1 year and 2 year actuarial survival rates of 71 per cent and 57 per cent respectively. In Europe, PSC is the third commonest indication for transplantation in adults with 1 and 3 year actuarial survival rates of 62·1 per cent and 52·6 per cent respectively in 148 patients[18].

Previous surgery on the biliary tree carries a poor outcome if followed by OLT (seven of eight patients who had had surgery died). In contrast, one of nine patients without previous surgery died. Previous biliary surgery should be regarded as a relative contraindication for transplantation. Increased blood transfusion requirements, the hazardous mobilization of the recipient liver because of adhesions and the presence of low grade sepsis contribute to the increased risk.

A diagnostic and management dilemma occurs when hepatobiliary malignancy has to be excluded as seen in four patients (8 per cent) in this series. Malignancy was only confirmed after transplantation in two and at laparotomy for transplantation in one. The Pittsburgh group[13] report a similar experience with 9·9 per cent of their patients with cholangiocellular carcinoma.

Skolkin *et al.*[19] described patients with PSC treated by percutaneous transhepatic cholangioplasty and external stent placement. This is a technically difficult procedure, with a significant re-stenosis rate, a high incidence of sepsis and poor tube tolerance. Repeated ERCP manipulation of biliary strictures is associated with complications (seven of 13 patients in this series). Bacterial colonization of the biliary tree may occur and make subsequent liver transplantation hazardous.

Helzberg *et al.*[20] in a retrospective study of 53 patients with PSC and a 30-year follow-up showed that hepatomegaly and a raised serum bilirubin were independent variables predictive of a poor outcome. Lebovics *et al.*[14] studied 38 patients with PSC over 6·3 years and a 4 × total bilirubin was associated with a poor outcome ($P<0{\cdot}05$). As in primary biliary cirrhosis[21], log serum bilirubin was the single most important prognostic factor in predicting survival. This study confirms that bilirubin is an important prognostic variable.

The management of PSC needs re-evaluating. Information collected prospectively in large multicentre studies is needed to provide a better understanding of the disease. With continuing uncertainty regarding the natural history of PSC, treatment schedules should have a schematic approach. In the asymptomatic patient, management should be conservative. ERCP manipulation is preferable to biliary surgery for localized distal disease in the non-cirrhotic, and any therapy which compromises eventual transplantation should be avoided. For progessive diffuse PSC and deteriorating liver function, early assessment for liver transplantation should be considered.

Adverse features which raise questions about management have been identified. PSC is being diagnosed more frequently and is usually associated with inflammatory bowel disease. It has a poorly defined aetiology and prognosis and medical and surgical treatment options are uncertain. These patients, many of whom are young, should be carefully assessed by medical and surgical specialists with experience of PSC. Future options should be carefully evaluated before any surgical procedure is undertaken and early consultation with a transplant centre should occur.

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References

1. Summerfield J. Primary sclerosing cholangitis. *Postgrad Med J* 1983; **59**: 99–105.
2. Delbet P. Retrecissement du choledoque: cholecystoduodenostomie. *Bull Mem Soc Nat Chirurg* 1924; **50**: 1144–6.
3. Wagner A. Azathioprine treatment in primary sclerosing cholangitis. *Lancet* 1971; **ii**: 663–4.
4. Myers RN, Cooper JH, Padis N. Primary sclerosing cholangitis: complete gross and histologic reversal after long-term steroid therapy. *Am J Gastroenterol* 1970; **53**: 527.
5. Leiser A, Kadish U. Beneficial effect of colchicine in a case of sclerosing cholangitis. *Am J Med Sci* 1986; **291**: 416–18.
6. La Russo NF, Wiesner RH, Ludwig J, MacGarty RL, Beaver SJ, Zingmeister AR. Prospective trial of penicilliamine in primary sclerosing cholangitis. *Gastroenterology* 1988; **95**: 1036–42.
7. Polter DE, Gruhl V, Eigenbrodt EH, Combes B. Beneficial effects of cholestyramine in sclerosing cholangitis. *Gastroenterology* 1980; **79**: 329–33.
8. Allison MC, Burroughs AK, Noone P, Summerfield JA. Biliary lavage with corticosteroids in primary sclerosing cholangitis – a clinical, cholangiographic and bacteriological study. *J Heptol* 1986; **3**: 118–22.
9. Pitt HA, Thompson HH, Tompkins RK, Longmire WP. Primary sclerosing cholangitis: results of an aggressive surgical approach. *Ann Surg* 1982; **3**: 259–68.
10. Cameron JL, Gayler BW, Herlong HF, Maddrey WC. Sclerosing cholangitis: biliary reconstruction with silastic trans-hepatic stents. *Surgery* 1983; **94**: 324–30.
11. Cameron JL, Pitt HA, Zinner J *et al.* Resection of hepatic duct bifurcation and trans-hepatic stenting for sclerosing cholangitis. *Ann Surg* 1988; **207**: 614–22.
12. Krige JEJ, Terblanche J, Harries Jones EP, Bonman PC. Primary sclerosing cholangitis: biliary drainage and duct dilation. *Br J Surg* 1987; **74**: 54–7.
13. Marsh JW Jr, Iwatsnki S, Makowka L *et al.* Orthotopic liver transplantation for primary sclerosing cholangitis. *Ann Surg* 1988; **207**: 21–5.
14. Lebovics E, Palmer M, Woo J, Schaffner F. Outcome of primary sclerosing cholangitis. *Arch Intern Med* 1987; **147**: 729–31.
15. Wiesner RH, Grambsch P, La Russo NF, Dickson ER. Is primary sclerosing cholangitis a progressive disease or not? *Hepatology* 1988; **8**: 970–1.
16. Cangemi JR, Wiesner RH, Beaver SJ *et al.* Effect of proctocolectomy for chronic ulcerative colitis on the natural history of primary sclerosing cholangitis. *Gastroenterology* 1989; **96**: 790–4.
17. Thompson JS, Wood RP, Burnett DA, Byers WS, Rihkers LF. The role of non-transplant procedures for sclerosing cholangitis. *Am J Surg* 1988; **156**: 506–8.
18. The European Liver Transplant Registry. July 1989. H. Bismuth, Hôpital Paul Brousse, Villejuif, France.
19. Skolkin MD, Alspaugh JP, Casarella WJ, Chuang VP, Galambos JT. Sclerosing cholangitis – palliation with percutaneous cholangioplasty. *Radiology* 1989; **170**: 199–206.
20. Helzberg JH, Petersen JM, Boyer JL. Improved survival with primary sclerosing cholangitis. *Gastroenterology* 1987; **92**: 1869–75.
21. Christensen E, Neuberger J, Crowe J *et al.* Beneficial effect of azathioprine and prediction of prognosis in primary biliary cirrhosis. *Gastroenterology* 1985; **89**: 1084–91.

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Effects of relief of biliary obstruction on mononuclear phagocyte system function and cell mediated immunity

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Obstructive jaundice causes depression of immune system function but it is unclear at present how rapidly immune function recovers after relief of biliary obstruction. To address this issue, we studied 218 Sprague-Dawley rats with common bile duct obstruction. Mononuclear phagocyte function, cell mediated immune function, portal–systemic shunt fraction, liver function tests, and liver histology were evaluated in normal (sham) rats, obstructed rats, and at weekly intervals after relief of biliary obstruction. Hepatic uptake of radiolabelled bacteria was 82 per cent in sham rats and 66 per cent in rats 21 days after CBD obstruction ($P<0.05$)*. Phagocytic activity returned to normal within 7 days after choledochoduodenostomy. Cell mediated immunity, measured by skin graft rejection, was significantly prolonged in the obstructed group* ($P<0.05$) *but had returned to normal 7 days after biliary diversion. Return of hepatocellular function, as measured by liver function tests, paralleled recovery of immune function. This study demonstrates prompt recovery of the immune system after internal biliary drainage for obstructive jaundice. This finding is in contrast to previous studies that demonstrated persistent immune suppression months after biliary diversion. These data may have implications concerning the usefulness of internal biliary drainage before surgery in patients with obstructive jaundice.*

The patient with biliary obstruction, affected by malnutrition, sepsis or malignancy, poses a difficult treatment problem and represents a significant challenge to the clinician. Surgery to resect or bypass the obstructing lesion is associated with a significant incidence of complications. Renal failure, gastrointestinal haemorrhage, wound dehiscence, fistula formation and sepsis are more likely to occur after surgery performed in the presence of biliary obstruction[1,2]. The immunosuppressive effects of obstructive jaundice are well defined[3–9] and widely accepted. Recovery of immune function after biliary drainage, however, is not clearly documented. This study is designed to characterize the effects of obstructive jaundice and subsequent relief of biliary obstruction on mononuclear phagocyte function and on cell mediated immunity.

Materials and methods

In all 218 adult male Sprague-Dawley rats (300–400 g) were entered into the study (*Table 1*), adhering to regulations set forth by the Southwestern Medical Center Institutional Review Board for Animal Research. Under methoxyflurane inhalation anaesthesia, 171 rats underwent laparotomy with common bile duct ligation and division. Forty-seven rats had laparotomy with isolation and manipulation of the common bile duct without ligation and served as sham operated controls. At 21 days after bile duct obstruction, choledochoduodenostomy was performed in 122 rats to achieve biliary diversion as described by Ryan *et al.*[10]. Rats received cefazolin 17 mg/kg just before laparotomy and were resuscitated with Ringer's lactate 50 ml/kg subcutaneously immediately after surgery. The 49 rats with common duct ligation but without biliary diversion were evaluated 21 days after ligation as obstructed controls (CDL group). Cell mediated immunity and function in the mononuclear phagocyte system were evaluated in sham controls, obstructed controls, and at weekly intervals after biliary diversion to document immune suppression and subsequent return of immune function. Portal–systemic shunting was measured in each group to determine how changes in hepatic portal flow affected measurement of phagocytic function. Serum liver function tests and liver histology were evaluated in each group.

Mononuclear phagocyte system function

To evaluate phagocytic activity in the mononuclear phagocyte system, rats were injected with radiolabelled *Escherichia coli*. *E. coli* were prepared by incubation with ^{75}Se-selenomethionine in methionine-free broth to allow incorporation of the radioisotope. This technique produced an injectate of 4.6×10^9 live *E. coli* per ml with one of every 70 bacteria radiolabelled. An innoculum of 1 ml was injected into the lateral tail vein of each animal on the day designated for bacterial challenge (sham rats, CDL rats and rats 7, 14, 21 or 28 days after biliary diversion). Animals were killed 30 min after injection. Organs comprising the reticuloendothelial system (liver, lungs and spleen) were harvested and radioactivity was determined using a γ-scintillation counter (Packard, model 5320, Richardson, Texas, USA). Relative phagocytic uptake of the injected bacteria was calculated from the total radioactivity of the injectate and the radioactivity of each organ:

$$\text{Percentage bacterial uptake} = \frac{\text{radioactivity in individual organ}}{\text{total radioactivity injected}} \times 100$$

Previous studies by Dunn *et al.*[3] using this technique demonstrated that more than 98 per cent of injected bacteria were cleared within 30 min of injection and that phagocytic function was significantly depressed in the liver of obstructed animals. This technique allows recovery of 94 per cent of the injectate by harvesting liver, lungs and spleen[3].

Determination of portal–systemic shunt

Because biliary obstruction leads to cirrhosis, portal hypertension and portal–systemic shunting, we were concerned that decreased hepatic uptake of bacteria may reflect decreased bacterial delivery to the liver because of decreased blood flow, rather than truly impaired phagocytic function. Portal systemic shunting was measured in separate animals in each treatment group (sham, CDL, and 7, 14 and 28 days after diversion). According to the method described by Chojkier and Groszmann[11], laparotomy was performed and each spleen was injected

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Table 1 *Animal utilization*

218 rats	
47 shams	7 shams for liver function studies and histology
	10 shams for portal flow studies
	16 shams for bacterial uptake studies
	14 shams for skin grafting
171 rats Common duct ligation	
49 rats CDL group	12 CDL rats for bacterial uptake studies
	10 CDL rats for portal flow studies
	14 CDL rats for liver function studies and histology
	13 CDL rats for skin grafting
122 rats Choledochoduodenostomy	
39 rats 7 days after biliary diversion	15 rats for bacterial uptake studies
	10 rats for portal flow studies
	5 rats for liver function studies and histology
	9 rats for skin grafting
25 rats 14 days after biliary diversion	10 rats for bacterial uptake studies
	10 rats for portal flow studies
	5 rats for liver function studies and histology
25 rats 21 days after biliary diversion	12 rats for bacterial uptake studies
	13 rats for skin grafting
29 rats 28 days after biliary diversion	5 rats for bacterial uptake studies
	5 rats for portal flow studies
	5 rats for liver function studies and histology
	14 rats for skin grafting
4 rats 42 days after biliary diversion	4 rats for liver function studies and histology

CDL, common duct ligation

with 0·2 ml of a suspension of ^{113}Sn-labelled 15 μm microspheres (approximately 30000 microspheres in 0·2 ml). After 15 min, animals were killed and radioactivity was measured in the liver, lungs, spleen and kidneys using the γ-scintillation counter to determine the ultimate distribution of the injected microspheres. Portal-systemic shunting was expressed as the percentage of microspheres entering the systemic circulation that lodged in the pulmonary capillary bed. Shunting was calculated as:

$$\text{Percentage shunt} = \frac{\text{lung radioactivity}}{\text{lung radioactivity} + \text{liver radioactivity}} \times 100$$

Liver function tests and histology

To evaluate changes in liver function tests, alkaline phosphatase, serum glutamic pyruvic transaminase (SGPT), total bilirubin, total protein, albumin, and γ-glutamyl transferase (GGT) levels were assayed in blood taken from sham and obstructed animals as well as animals 7, 14, 28 and 42 days after choledochoduodenostomy. Each of these animals was killed after blood samples were taken and the liver was preserved for histopathological examination.

Cell mediated immunity

Allogeneic skin graft rejection was used as an *in vivo* measure of T cell function. Donor skin was harvested from the abdomen of healthy outbred Sprague-Dawley rats and was grafted on to the back of rats in sham and obstructed groups and rats 7, 14 and 28 days after choledochoduodenostomy. Grafts were uniformly 15 × 15 mm in size. A rigid dressing was applied and left in place for 10 days to allow graft adherence. After the dressing was removed, the surface area of the skin graft was measured daily as described by Keane *et al.*[8]. Graft survival was recorded as the number of days required for the graft surface area to be reduced by 80 per cent or the number of days until the animal died with a viable skin graft. We were compelled to include survival of the animal as a measure of graft survival because of the high mortality rate in the CDL group (obstructed controls). Nine of 13 animals in this group died from unrelieved biliary obstruction before skin graft rejection occurred.

Statistical analysis

Statistical analysis of the resulting data was completed using the Student Neuman Keuls test for comparison of multiple independent groups. Results are expressed as the mean(s.e.m.).

Results

Mononuclear phagocyte system function

Sham rats, those with an intact biliary system, demonstrated 82 per cent uptake of injected *E. coli* in the liver, 4 per cent in the lung and 12 per cent in the spleen. Rats with common bile duct obstruction of 3 weeks duration (CDL) demonstrated a decrease in hepatic uptake (from 82 per cent to 66 per cent) with a reciprocal increase in pulmonary uptake (from 4 per cent to 22 per cent). After choledochoduodenostomy, hepatic and pulmonary uptake returned to preobstructive levels within 7 days of diversion and remained at this level in groups studied 14, 21 and 28 days after biliary diversion (*Table 2*). Splenic uptake was not changed after ductal ligation or diversion. The differences in hepatic and pulmonary uptake values for sham, CDL, and shunted groups were statistically significant ($P < 0{\cdot}05$).

Portal–systemic shunt

Portal–systemic shunt fractions in sham animals were small (2·0(1·0) per cent) and confirmed previous studies of shunts in normal rats[11]. Animals in the CDL group developed significant shunting of portal flow after 21 days of biliary obstruction (46·6(13·1) and shunt fractions did not improve ($P < 0{\cdot}05$) after choledochoduodenostomy (*Figure 1*). Radioactivity in the kidneys was negligible, indicating that all microspheres were trapped in the first capillary bed encountered (liver or lungs) and providing evidence for the validity of the technique.

Liver function studies

Alkaline phosphatase, SGPT, total bilirubin, total protein,

Table 2 *Uptake of injected bacteria*

Group		Liver	Lung	Spleen
Sham	($n = 16$)	81·9(1·0)	4·2(0·7)	12·2(0·8)
CDL	($n = 12$)	66·2(6·2)*	22·2(5·4)*	10·7(0·7)
7 days	($n = 15$)	80·1(3·8)	5·5(2·1)	13·7(1·9)
14 days	($n = 10$)	82·1(1·6)	1·7(0·3)	15·1(1·4)
21 days	($n = 12$)	80·0(1·8)	2·2(0·4)	17·4(1·6)
28 days	($n = 5$)	86·0(1·6)	1·5(0·3)	11·9(1·4)

Values are mean(s.e.m.). CDL, common duct ligation group; 7, 14, 21 and 28 days, length of time these groups were studied after choledochoduodenostomy. * $P < 0{\cdot}05$

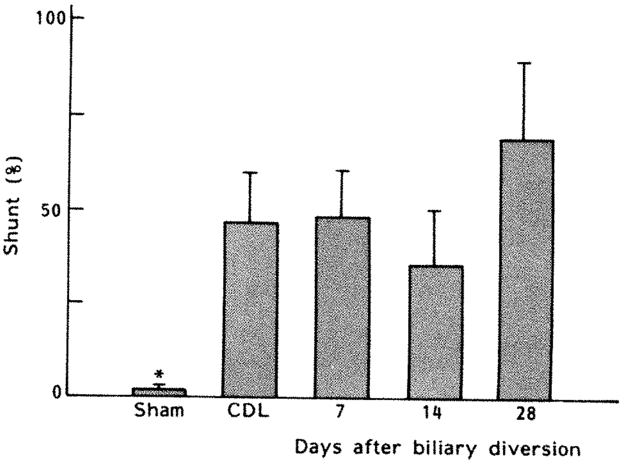

Figure 1 *Portal–systemic shunting is significantly elevated with biliary obstruction and does not normalize after diversion.* n = *10 in each group except 28 days after diversion where* n = *5.* * P < *0·05*

Table 3 *Liver function studies*

	Total bilirubin (mg/l)	SGPT (units/l)	[GGT] (units/l)	Albumin (g/l)	Total protein (g/l)	Alkaline phosphatase (units/l)
Sham	1(0) (*n* = 7)	100(15) (*n* = 5)	5·4(0·4) (*n* = 5)	33·6(0·2) (*n* = 7)	53·5(0·2) (*n* = 7)	428(40) (*n* = 9)
CDL	618(0·9)* (*n* = 14)	434(28)* (*n* = 7)	78·7(10)* (*n* = 9)	29·3(0·1) (*n* = 13)	51·5(1·5) (*n* = 14)	574(21) (*n* = 13)
7 days (*n* = 5)	3(0·8)	75(18)	9·8(9)	30(2)	67(3)	475(130)
14 days (*n* = 5)	1(0·2)	50(12)	0·6(0·6)	29(1)	69(3)	280(29)
28 days (*n* = 5)	1(0·2)	80(9)	1·0(0·7)	30(1)	65(2)	452(82)
42 days (*n* = 4)	1(0·2)	32(11)	0·2(0·02)	32(1)	69(2)	339(88)

Values are mean(s.e.m.). CDL, common duct ligation group; 7, 14, 28 and 42 days, length of time these groups were studied after biliary diversion. $^*P<0\cdot05$

albumin and γ-glutamyl transferase levels were assayed in sham and CDL animals and in animals 7, 14, 28 and 42 days after biliary diversion (*Table 3*). Total bilirubin, SGPT and GGT levels were all significantly elevated ($P<0\cdot05$) in the CDL group and all had returned to preobstruction levels within 7 days of biliary diversion. Albumin, total protein and alkaline phosphatase levels did not change significantly during the study period.

Histology

Histopathological examination was performed on livers from rats in sham and obstructed groups and rats 7, 14, 28 and 42 days after biliary diversion. Sham rats had normal liver architecture. The livers of obstructed rats demonstrated congestion, inflammatory infiltrates, bile duct proliferation and periportal fibrosis. After choedochoduodenostomy, histological findings were similar but decreased in severity after relief of obstruction. Periportal fibrosis and mild inflammatory infiltrates persisted 42 days after biliary diversion.

Cell mediated immunity

Skin graft rejection occurred 17·1(0·4) days after grafting in the sham control group. Graft survival was significantly prolonged ($P<0\cdot05$) at 20·0(1·0) days in the CDL group and returned to normal within 7 days of choledochoduodenostomy (*Figure 2*).

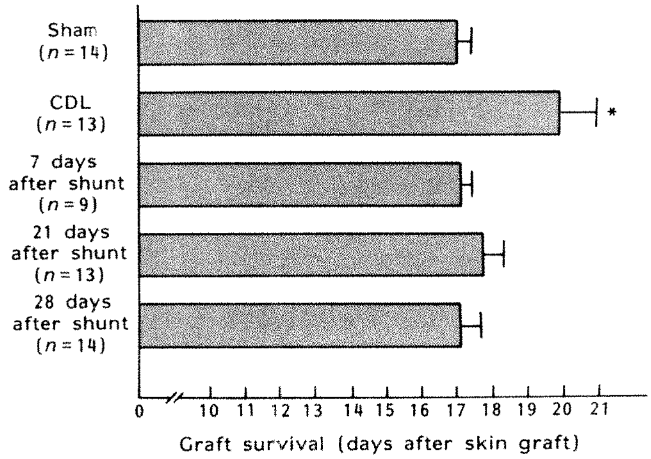

Figure 2 *Cell mediated immunity is significantly depressed after biliary obstruction but returns to normal within 7 days of biliary diversion (post-shunt).* $^*P<0\cdot05$

Discussion

Obstruction of the extrahepatic biliary tree produces profound depression of multiple components of the immune system. Impairment of cell mediated immunity has been studied extensively. Pinto and Kaplun demonstrated depressed T cell function (in spite of normal T cell numbers) *in vitro* and *in vivo* after common bile duct ligation in mice[4]. Vane *et al.*[5] and Roughneen *et al.*[6] both demonstrated *in vitro* T cell dysfunction, using a mitogen stimulation assay, that persisted for prolonged periods (up to 3 months) after relief of biliary obstruction. In contrast, our study demonstrates prompt recovery of T cell function within 7 days of biliary diversion, as measured *in vivo* by an allogeneic skin graft rejection assay. It is important to note that our graft survival of 20·0(1·0) days for the obstructed animals included nine rats that died before graft rejection. Keane *et al.*[8] demonstrated skin allograft survival of 35(11) days in Sprague-Dawley rats with obstructive jaundice who lived long enough to reject their grafts. Although graft survival for jaundiced rats is significantly prolonged as reported herein, it is clear that graft survival would have been greater, and the recovery more impressive after biliary drainage, if our obstructed rats had survived long enough to reject the skin graft. Differences between our results and those described by Vane *et al.* may be a species dependent factor as rabbits were used in their study. Roughneen *et al.* used rats, however, and presented data that will permit comparison of *in vitro* and *in vivo* results. Vane *et al.*[5] also showed that hepatic phagocytic function in the rabbit, measured by disappearance of technectium-99 sulphacolloid, was depressed after biliary obstruction and did not return to normal until 6 months after restoration of biliary-enteric continuity. Our study confirms previous findings of impaired phagocytic function in obstructive jaundice by demonstrating a significant decrease in hepatic sequestration of injected bacteria from 82 per cent to 66 per cent. Unlike previous studies, we have demonstrated rapid recovery of hepatic phagocytic function after relieving biliary obstruction. Seven days after choledochoduodenostomy, hepatic uptake returned to 80·1 per cent, a value no different from sham values but significantly different from values in obstructed animals. The increase in the percentage of bacteria trapped in the lung (4 per cent in sham, 22 per cent in obstructed rats) may at first seem an appropriate compensatory response. However, this increase represents a greater than five-fold increase in the bacterial load to be handled by the alveolar macrophage mass and may well overwhelm the bacterial killing capacity of that system. Evidence for reduced pulmonary bactericidal activity in obstructive jaundice was provided by Dunn and Horton[12] who showed a 4-log-fold increase in viable bacteria in the lungs of rats with obstructive jaundice 24 h after innoculation when compared with sham animals that had no viable bacteria present in the lungs after 24 h. Katz *et al.*[9] have demonstrated a similar compensatory increase in pulmonary phagocytosis after common bile duct obstruction and also showed that bacterial survival after phagocytosis was considerably greater in the lung than in the liver. Katz *et al.* suggested that, although the lung can trap more bacteria in the presence of jaundice induced Kupffer cell dysfunction, the alveolar macrophage may have an impaired bactericidal capacity.

Determination of shunt fraction was necessary to prove that changes in phagocytic activity did not merely reflect changes in blood flow. Measurement of portal–systemic shunting demonstrated that while phagocytic activity in the liver recovered after biliary diversion, shunt fraction did not. Persistence of portal systemic shunting may be the result of slowly resolving periportal fibrosis seen on histological examination of the liver.

Serum liver function tests demonstrated a recovery of hepatocellular function that occurred as rapidly after choledochoduodenostomy as did phagocytic function. The two may, in fact, be interdependent. Curran *et al.*[13] have shown that Kupffer cell mediated tumour cytostasis depends on intact hepatocyte function. The same relationship may exist for maximal phagocytosis and bactericidal activity by the Kupffer cell.

Depressed immune function accompanying obstructive jaundice places the patient at significant risk for postoperative complications[1,2]. The direct effects of impaired phagocytosis and cell mediated immunity on the patient's response to sepsis are obvious, but there are serious indirect effects on the patient as well. Decreased hepatic clearance of endotoxin absorbed from the intestinal lumen in patients with obstructive jaundice has been implicated in the increased incidence of acute renal failure observed in patients with biliary obstruction[14,15]. Preoperative biliary drainage has been proposed as a means to decrease postoperative morbidity. Percutaneous transhepatic biliary drainage was investigated but has largely been abandoned because of high complication rates[2,16]. Internal biliary drainage has been shown experimentally to be more effective than external drainage in allowing an adequate immune response to sepsis[17]. Lygidakis *et al.*[18], in a prospective randomized study, reported decreased post-operative complications in 19 patients who received endoscopic transampullary stent placement for biliary drainage before surgery for carcinoma of the head of the pancreas.

Our study provides evidence for rapid normalization of phagocytic function and cell mediated immunity after biliary drainage in obstructive jaundice. In patients, these beneficial effects may be more evident after endoscopic stent drainage is accomplished without the associated morbidity of the percutaneous approach. Clinical trials are warranted to define the rate of immune system recovery and to determine the efficacy of preoperative endoscopic biliary drainage in the management of patients with obstructive jaundice.

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References

1. Armstrong CP, Dixon JM, Taylor TV, Davies GC. Surgical experience of deeply jaundiced patients with bile duct obstruction. *Br J Surg* 1984; **71**: 234–8.
2. Pellgrini CA, Allegra P, Sougard FS, Way LW. Risk of biliary surgery in patients with hyperbilirubinemia. *Am J Surg* 1987; **154**: 111–17.
3. Dunn CW, Horton JW. Impairment of mononuclear-phagocyte system function in obstructive jaundice. *FASEB J* 1989; **3**: A930.
4. Pinto M, Kaplun A. Immune status in mice with experimental biliary obstruction. *Clin Immunol Immunopathol* 1980; **16**: 396–405.
5. Vane DW, Redlich P, Weber T, Leapman S, Siddiqui AR, Grosfeld JL. Impaired immune function in obstructive jaundice. *J Surg Res* 1988; **45**: 287–93.
6. Roughneen PT, Gouma DJ, Kulkarni AD, Fanslow WF, Rowlands BJ. Impaired specific cell mediated immunity in experimental biliary obstruction and its reversibility by internal biliary drainage. *J Surg Res* 1986; **41**: 113–25.
7. Pain JA. Reticulo-endothelial function in obstructive jaundice. *Br J Surg* 1987; **74**: 1091–4.
8. Keane RM, Collins PB, Johnson AH, Bouchier Hayes D. Delayed homograft rejection following common bile duct ligation: *in vivo* evidence that obstructive jaundice is immunosuppressive. *Irish J Med Sci* 1986; **155**: 143–6.
9. Katz S, Grosfeld JL, Gross K *et al.* Impaired bacterial clearance and trapping in obstructive jaundice. *Ann Surg* 1984; **199**: 14–20.
10. Ryan CJ, Than T, Blumgart LH. Choledochoduodenostomy in the rat with obstructive jaundice. *J Surg Res* 1977; **23**: 321–31.
11. Chojkier M, Groszmann RJ. Measurement of portal-systemic shunting in the rat using gamma-labeled microspheres. *Am J Physiol* 1981; **240**: 6371–5.
12. Dunn CW, Horton JW. Muramyl dipeptide improves mononuclear phagocyte system function in obstructive jaundice. *J Surg Res* 1990; **48**: 249–53.
13. Curran RD, Billiar TR, Kispert PH, Bentz BG, Simmons RL. Hepatocytes enhance Kupffer cell mediated tumor cell cytostasis *in vitro*. *Surgery* 1989; **106**: 126–32.
14. Cahill CJ, Pain JA, Bailey ME. Bile salts, endotoxin and renal function in obstructive jaundice. *Surg Gynecol Obstet* 1987; **165**: 519–22.
15. Bailey ME. Endotoxin, bile salts, and renal function in obstructive jaundice. *Br J Surg* 1976; **63**: 774–8.
16. Joseph PK, Biger LS, Sprayregen SS, Gliedman ML. Percutaneous transhepatic biliary drainage: results and complications in 81 patients. *JAMA* 1986; **255**: 2763–7.
17. Gouma DJ, Coelho JCU, Schlegel JF *et al.* The effect of preoperative internal and external biliary drainage on mortality of jaundiced rats. *Arch Surg* 1987; **122**: 731–4.
18. Lygidakis NJ, van der Heyde MN, Lubbers MJ. Evaluation of preoperative biliary drainage in the surgical management of pancreatic head carcinoma. *Acta Chir Scand* 1987; **153**: 665–8.

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Effect of percutaneous interstitial thermal laser on normal liver of pigs: sonographic and histopathological correlations

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Tumour necrosis can be induced by interstitial application of low power laser light, which causes thermal damage to the tissue. In normal pig liver the effects were studied of low power Nd:YAG laser light (continuous wave; 1·5 W, 10 min, wavelength 1064 nm), administered percutaneously via a 600 μm fibre. Ultrasound images were compared with histopathological findings. Histopathology showed induction of sharply demarcated lesions with a mean diameter of 10–15 mm (days 0 and 7), consisting of coagulative necrosis. Healing of the lesion occurred by granulation, fibrosis and removal of cell debris. Lesions could not be seen by week 4, which suggests complete regeneration. Ultrasonography showed a good correlation with histopathology, especially at 1 week when different histopathological tissue layers could be discriminated by ultrasonography. It is concluded that thermal lesions in liver can be induced via a percutaneous route and that ultrasound imaging is useful in monitoring the lesions during and after the procedure.

The purpose of the study was to make thermal lesions in the liver by laser via a percutaneous route and to correlate ultrasound images with histopathological findings. To our knowledge this is the first study of this kind in which laser light is applied percutaneously.

The use of lasers to induce tumour necrosis is well known, for instance in the gastrointestinal tract and the bronchial tree[1–3]. Here endoscopic techniques were used and high power laser light was applied to the surface of the tumour. In interstitial laser treatment laser light is applied more deeply by inserting an optical fibre directly into the tissue, for example into the liver. In animal experiments the histopathological effects of interstitial laser treatment in liver and other organs have been studied[4–9]. Laparotomy for fibre introduction into the liver and/or peroperative ultrasound imaging has been used. Low power laser light of 1–5 W was effective in inducing necrotic lesions after a 3–15 min exposure[4,8,9]. Magnetic resonance imaging has also been used to monitor laser effects in tissue[10].

For clinical applications a percutaneous method[11] is preferable to an operative one[12], in which case ultrasound guidance is very useful.

Materials and methods

Laser treatment

A percutaneous puncture was made using a 14 Fr gauge needle with stylet and ultrasound guidance (Aloka 630, 5·5 MHz linear array probe). An optical fibre (core diameter 600 μm) was inserted through the needle, with the tip protruding 10 mm. For each lesion low power laser light of 1·5 W was administered for 10 min (continuous wave Neodynium:YAG, CL 860 of Surgical Laser Technologies, wavelength 1064 nm). In each animal three different lesions were made during the same experiment, giving 12 lesions in total.

Animal techniques

The experimental animals were four female pigs of the Pure Yorkshire breed (20–30 kg, age 8–9 weeks). On the day before and after laser treatment they received only water, otherwise they were kept on a standard diet. Before laser treatment, Stresnil®, 0·5 ml/kg (azaperone at a concentration of 40 mg/ml, Janssen Pharmaceutica BV, Tilburg, The Netherlands) and atropine sulphate (dose 0·01 mg/kg, AUV CV, Cuijck, The Netherlands) were administered intravenously, followed by intubation and artificial ventilation with nitrous oxide, oxygen and 1% halothane. During follow-up ultrasonography the pigs were sedated with nitrous oxide and halothane by a mask. The pigs were killed by intravenous injection of a high concentration of pentobarbital (200 mg/ml; Euthasaat®, Apharmo, Arnhem, The Netherlands).

Follow-up ultrasound scanning

Follow-up ultrasound scans were performed immediately and at days 7, 14, 21 and 28 after laser treatment. The scanning plane was directed through the centre of the lesions. The extent of the long and short axis of the visible lesions and of their concentric hyperechoic and hypoechoic layers (if present) were measured and compared with histological measurements of the same axes.

Histopathology

The pigs were killed for histopathological examination at 1 h and at days 7, 14 and 28 after laser treatment. Pieces of liver tissue, measuring about 15 cm^3 containing the lesions, were excised from the liver. These tissue specimens were fixed in 3·8 per cent formaldehyde for 48 h, dehydrated in graded ethanol solutions and xylene and then embedded in paraffin. Sections 5 μm thick were cut for light microscopy with the plane through the centre of the lesion and then stained with haematoxylin and eosin. The qualitative histopathological study consisted of examination of the inflammatory and tissue repair processes. The quantitative study consisted of measurements of the long and short axes of the concentric layers of the lesions by eyepiece micrometry.

Blood chemistry

Blood levels of the enzymes lactate dehydrogenase (LDH), alkaline phosphatase, serum glutaminate oxaloacetate transaminase (SGOT) and serum glutaminate pyruvate transaminase (SGPT) were measured as parameters of liver injury. Venous blood samples were taken immediately before treatment and at days 1, 2, 7, 14, 21 and 28 after treatment.

Results

Acute lesion

After 2 min of laser application the ultrasound image showed an echogenic lesion developing around the fibre tip. Small echogenic spots were seen moving away from the lesion and occasionally gas bubbles could be seen in the surrounding larger

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vessels. The lesions did not increase in size afer 6–8 min. Two minutes after laser treatment the remaining echogenic lesion was slightly smaller. Histopathology showed a sharply demarcated spherical to ellipsoid lesion. The centre of the lesion contained little carbonization and coagulation, and was surrounded by so-called vapour cavities. At the periphery of the lesion a broad zone of degenerating liver parenchyma was present, with lighter staining cytoplasm and condensed nuclei (*Figure 1*).

Day 7 lesion

At day 7 the ultrasound image showed a target-like lesion with an echogenic centre, surrounded by a broad hypoechogenic zone. The lesion was delineated from normal parenchyma by a narrow echogenic ring. Sometimes the echogenic centre showed acoustic shadowing.

Histopathologically and macroscopically the concentric nature of the lesions was confirmed. The centre of the lesion was unaltered compared with the acute lesion. Around the centre a broad zone of coagulative necrosis was now present. This zone was infiltrated by polymorphonuclear leucocytes. The lesion was demarcated from normal parenchyma by a narrow zone of fibrosis containing proliferating blood vessels, bile ductules and groups of histiocytes and giant cells. Iron deposits were indicative of removal of the parenchymal tissue debris by activity of these cells (*Figure 2*).

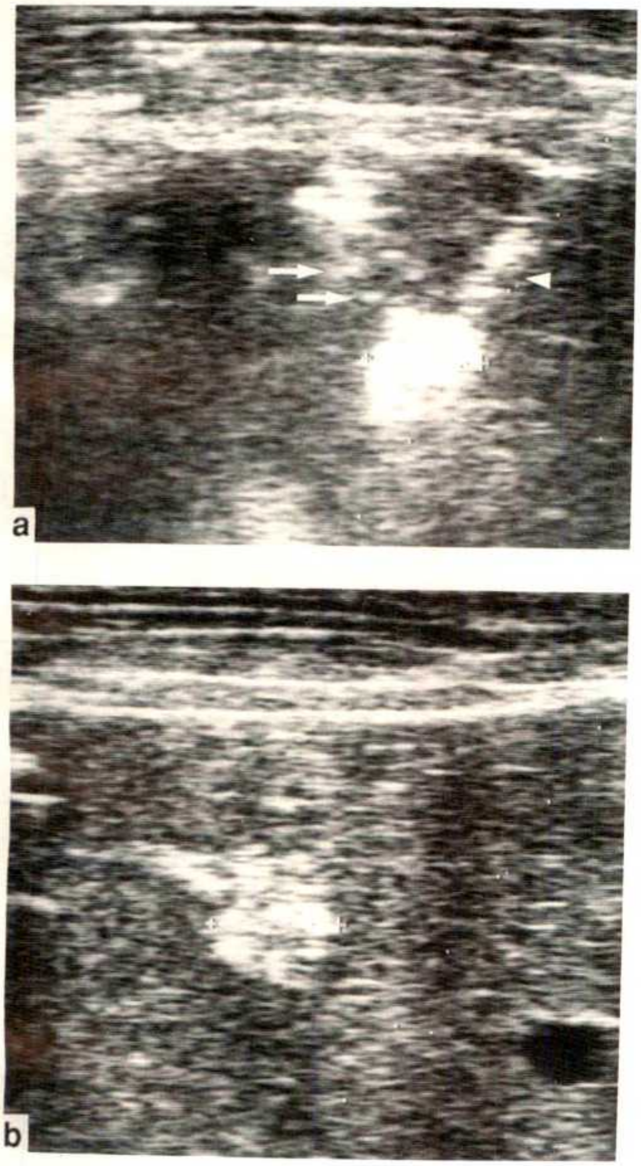

Figure 1 *Interstitial thermal laser lesion.* **a** *Ultrasound image during laser treatment, showing vapour bubbles (arrows) and needle tract (arrowhead).* **b** *Same lesion 2 min after laser treatment, somewhat smaller size (diameter 10 mm)*

Day 14 lesion

At day 14 ultrasonography showed smaller lesions which were echogenic and no longer had discernable layers. Histopathology showed a significant increase of the fibrotic zone into the lesions. In the necrotic centre the number of inflammatory cells was greatly diminished (*Figure 3*). One of the lesions could not be seen histopathologically at days 7 and 14. At 4 weeks none of the lesions could be seen by ultrasonography or histopathology. *Figure 4* shows the correlation between the diameters of ultrasonographic and histological lesions.

Levels of liver enzymes are shown in *Figure 5*.

Discussion

The percutaneous procedure to induce thermal lesions could be performed easily and ultrasonography clearly showed the development of lesions during laser application. The high echogenicity of the lesions may be caused by vaporization and cavity formation. Histopathologically, carbonization was minimal as expected from low power laser light[4], but its presence in the centre of the lesion suggests temperatures well above the boiling point of water. Initial coagulative necrosis around the carbonization zone was limited. The larger part of necrosis developed during the first week[13] and is probably caused by exposure to temperatures from the hyperthermia range (42–45°C) up to the lowest coagulation temperatures (about 60°C). Ultrasonography showed good correlation with histopathology, especially at 1 week when ultrasonography showed a target lesion and could discriminate fibrosis from coagulative necrosis. The small differences in lesion diameters between ultrasonography and histopathology can be explained by slightly different planes of measurement.

Healing of the lesions was rapid by an inflammatory reaction with fibrosis and regeneration. No lesion could be seen at 4 weeks, probably because of the small remaining size. Three lesions were initially very small (diameter 5–6 mm). These were located in the vicinity of large blood vessels. Presumably the flowing blood carried away much of the heat. Two of these lesions could not be seen at days 7 and 14.

Liver enzymes showed transient elevations during the first week, compatible with tissue injury. Only one animal survived longer and still had mild elevation of liver enzymes at day 28.

The qualitative histopathological and sonographic findings are in agreement with findings in other studies with low laser power in rat liver[4]. The maximal lesion diameters approximated to those in studies with high laser power (80 W, 10 s) delivered by a large bore handpiece (5 mm). In such studies ultrasonography showed more oedema and permanent scars were produced[7]. The cooling effect of blood flow in large vessels has more effect on lesion size than expected from low power studies in rat liver[4]. Therefore the optimal laser power in the vicinity of large vessel may be higher than the assumed 1·5 W.

Our conclusions are that deep thermal lesions in liver can be induced percutaneously by low laser power and that ultrasound screening is useful in monitoring this procedure. Ultrasound images show a good correlation with histopathological findings.

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The authors are indebted to C. W. J. Verlaan and K. Brandsma for their help with the animal techniques and F. Bos for his histotechnical expertise.

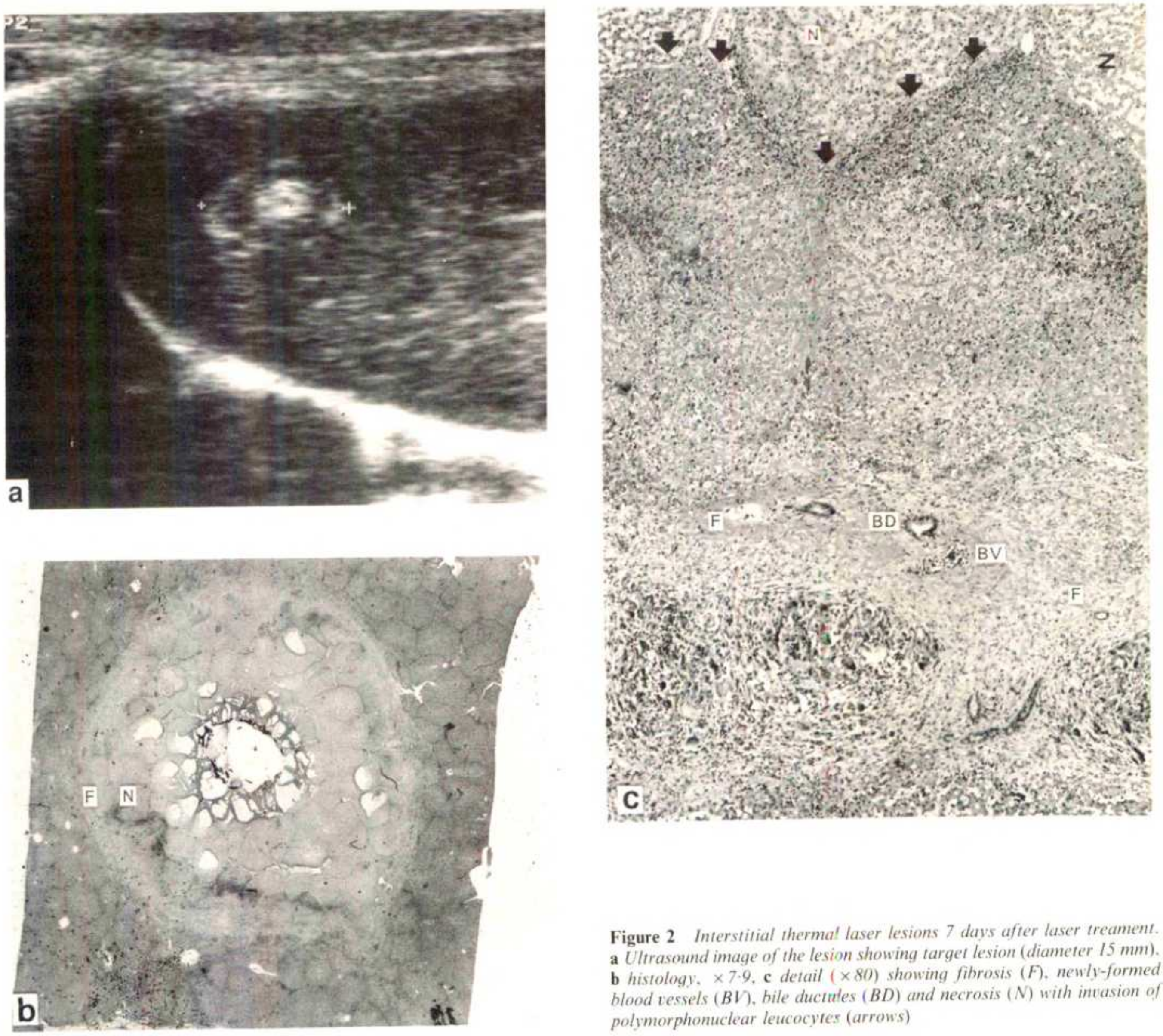

Figure 2 *Interstitial thermal laser lesions 7 days after laser treament.* **a** *Ultrasound image of the lesion showing target lesion (diameter 15 mm).* **b** *histology,* ×7·9, **c** *detail* (×80) *showing fibrosis (F), newly-formed blood vessels (BV), bile ductules (BD) and necrosis (N) with invasion of polymorphonuclear leucocytes (arrows)*

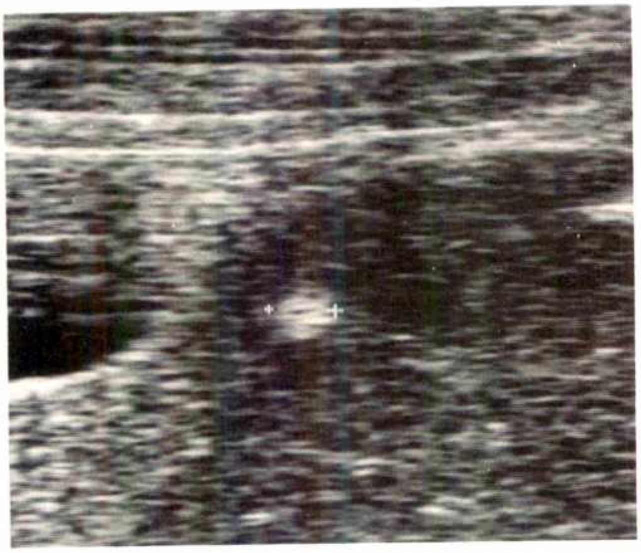

Figure 3 *Interstitial thermal laser lesion 14 days after laser treatment; ultrasound image lesion diameter 4 mm*

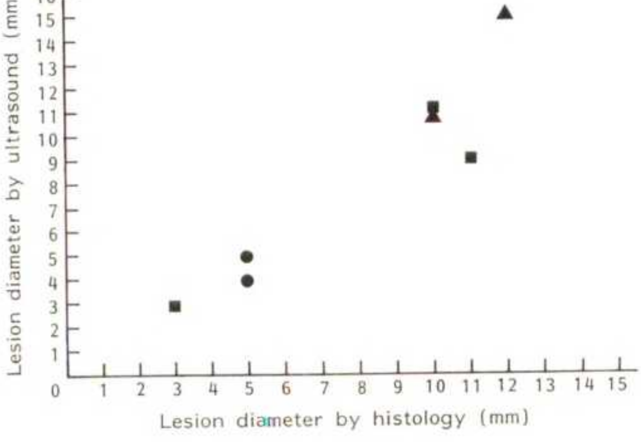

Figure 4 *Diameters of ultrasonographic* versus *histological single lesions (including fibrosis if present). Diameters are mean of short and long axes.* ■, *day 0;* ▲, *day 7;* ●, *day 14*

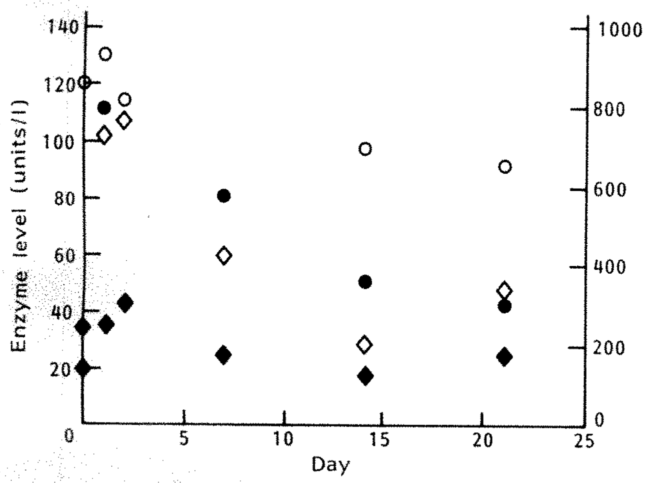

Figure 5 *Serum levels of liver enzymes just before (day 0) and after laser treatment. Data from the longest living pig.* ○, *alkaline phosphatase;* ◇, *serum glutamic oxaloacetic transaminase;* ◆, *serum glutamic pyruvic transaminase, left-hand scale.* ●, *LDH, lactate dehydrogenase, right-hand scale*

References

1. Mathus-Vliegen EMH, Tytgat GNJ. Laser photocoagulation in the palliative treatment of upper digestive tract tumours. *Cancer* 1986; **57**: 396–9.
2. Mathus-Vliegen EMH, Tytgat GNJ. Laser ablation and palliation in colorectal malignancy. *Gastroint Endoscopy* 1986; **32**: 393–6.
3. Dumon JF, Reboud E, Garbe L, Aucomte F, Meric B. Treatment of tracheobronchial lesions by laser photoresection. *Chest* 1982; **81**: 278–84.
4. Matthewson K, Coleridge-Smith P, O'Sullivan JP, Northfield TC, Bown SG. Biological effects of intrahepatic Nd YAG laser photocoagulation in rats. *Gastroenterology* 1987; **93**: 550–7.
5. Matthewson K, Barton T, Lewin MR. O'Sullivan JP, Northfield TC, Bown SG. Low power interstitial Nd YAG laser photocoagulation in normal and neoplastic rat colon. *Gut* 1988; **29**: 27–34.
6. Matthewson K, Barr H, Tralau C, Bown SG. Low power interstitial Nd YAG laser photocoagulation: studies in a transplantable fibrosarcoma. *Br J Surg* 1988; **76**: 378–81.
7. Godlewski G, Rouy S, Pignodel C *et al.* Deep localized Nd YAG laser photocoagulation in liver using a new water cooled and echoguided handpiece. *Lasers Surg Med* 1988; **8**: 501–9.
8. Steger AC, Matthewson K, Bown SG, Clark CG. Interstitial hyperthermia – a new therapy for intrahepatic neoplasms. *Gut* 1987; **28**: A1350.
9. Steger AC, Bown SG, Clark CG. Interstitial laser hyperthermia – studies in normal liver. *Br J Surg* 1988; **75**: 598 (Abstract).
10. Jolesz FA, Bleier AR, Jakab P, Ruenzel PW, Huttl K, Jako GJ. MR imaging of laser-tissue interactions. *Radioloy* 1988; **168**: 249–53.
11. Steger AC, Lees WR, Walmsley K, Bown SG. Interstitial laser hyperthermia: a new approach to local destruction of tumours. *Br Med J* 1989; **299**: 362–5.
12. Hashimoto D, Takami M, Idezuki Y. In-depth radiation therapy by YAG laser for malignant tumours in the liver under ultrasonic imaging. *Gastroenterology* 1985;**88**: 1663 (Abstract).
13. Nishimura Y, Jo S, Akuta K *et al.* Histological analysis of the effect of hyperthermia on normal rabbit hepatic vasculature. *Cancer Res* 1989; **49**: 4295–7.

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Acute necrotizing pancreatitis: management by planned, staged pancreatic necrosectomy/debridement and delayed primary wound closure over drains

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We reviewed our recent experience with management of 23 consecutive patients with acute necrotizing pancreatitis. All patients had documented necrotizing pancreatitis with parenchymal or peripancreatic necrosis. Our method of treatment has evolved from our previous approach of controlled open lesser sac drainage (marsupialization) to staged necrosectomy/debridement with delayed primary closure over drains. With this latter approach, hospital mortality was 4 of 23 patients (17 per cent), but significant morbidity still occurred in 12 of 23 patients (52 per cent). However, recurrent intra-abdominal abscess before discharge occurred in only one patient. We believe that this operative approach toward the severely ill patient with acute necrotizing pancreatitis who requires operative intervention will minimize the occurrence of intra-abdominal sepsis.

The recognition, appreciation, and management of severe, necrotizing pancreatitis has evolved dramatically over the past two decades. Recognition of the importance of pancreatic debridement (necrosectomy) has markedly improved survival over drainage alone. More recently, the natural history of necrotizing pancreatitis has been better elucidated, with appreciation of a spectrum of pancreatic necrosis, infected necrosis, and pancreatic abscess, each representing different pathophysiological stages in the evolution of the disease process[1–3]. Introduction of the technique of contrast-enhanced computed tomography (CT) has not only provided an earlier objective diagnosis of pancreatic parenchymal necrosis[4], but allowed its differentiation from non-necrotizing pancreatic and peripancreatic inflammation, a critical distinction which until now was not possible with routine CT[5–8]. This important distinction has made the term 'pancreatic phlegmon' confusing unless one further differentiates this peripancreatic inflammation from peripancreatic necrosis.

Our early experience with controlled open lesser sac drainage for pancreatic abscess was reported in 1986[9]. Since then, our technique of management has further evolved from open drainage to a staged necrosectomy with delayed primary closure over drains whenever possible. This report details our recent experience with the surgical management of severe necrotizing pancreatitis.

Patients and methods

The medical records of all consecutive patients undergoing surgical treatment for severe acute pancreatitis from 1986 through 1989 were reviewed. Only patients with operatively documented peripancreatic and pancreatic necrosis were selected for analysis. Careful distinction was made between patients with non-infected pancreatic necrosis, infected pancreatic necrosis, pancreatic abscess, and infected pseudocyst. This last group of patients was characterized by the presence of a single cavity of infected fluid without concomitant pancreatic and peripancreatic necrosis; these patients represent a different disease process with a different natural history and prognosis[10] and thus were excluded.

The first three groups included patients with peripancreatic and/or pancreatic parenchymal necrosis. The distinction between infected necrosis and (non-infected) pancreatic necrosis was made on the basis of cultures obtained either preoperatively by percutaneous needle aspiration and/or intraoperatively. Pancreatic abscess was differentiated from necrosis and infected necrosis by the presence of frank suppuration in addition to necrosis. Pancreatic parenchymal necrosis was evident by exposure of the superior mesenteric or splenic vein after necrosectomy or after a formal segmental pancreatic resection of histologically confirmed necrotic gland. Peripancreatic necrosis occurred when the pancreatic gland remained viable, either grossly or on histology of resected segments deemed 'necrotic' by the surgeon. These latter patients might have had patchy areas of of parenchymal necrosis but not involving a significant segment of the gland.

Multiple clinical and laboratory parameters were abstracted from the medical record. Patients were classified by three staging criteria: Ranson criteria[11], Imrie criteria[12], and APACHE II scoring[13]. Because our tertiary practice is in great part on a referral basis, we were not reliably able to score all patients with the Ranson and Imrie criteria at the onset of the acute necrotizing pancreatitis. Therefore, patients were classified using the above criteria either at the time of onset of pancreatitis (if they were initially managed at our institution from the time of onset of pancreatitis) or at the time of transfer to our institution with already established pancreatitis. We acknowledge that this deficit may have affected the predictive value of the Ransom and Imrie criteria. The APACHE II scoring system may be of better predictive value in those patients well into their disease process at the time of transfer to our institution[14].

Hospital morbidity and mortality (until discharge, not 30-day mortality) were carefully defined. The most likely aetiology of the pancreatitis was determined after review of the entire clinical picture. When no likely aetiology was evident, it was classified as indeterminant. Follow-up to date was obtained in all patients, either by return visit in the majority or by telephone interview, being careful to determine the incidence of recurrent intra-abdominal sepsis, gastrointestinal fistulae, and pancreatic morbidity (fistula, pseudocyst, exocrine and endocrine insufficiency, and recurrent pancreatitis).

Although the number of patients was small ($n = 23$), we correlated the clinical staging (Ranson, Imrie, APACHE-II) with postoperative morbidity statistically using a Spearman correlation.

Results

Patient group

From 1986 through 1989, 23 patients (18 men, 5 women) with necrotizing pancreatitis underwent operative management; five had non-infected necrosis, three had infected necrosis, and 15 had pancreatic abscess. Their mean age was 62 years (range, 42–84 years). The aetiology of pancreatitis was gallstone-

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Table 1 *Necrotizing pancreatitis: prognostic staging*

Staging classification*	No. of patients
Ranson criteria†[11]	
≤3	12 (55)
4–6	4 (18)
≥7	6 (27)
Imrie criteria†[12]	
≤3	11 (50)
4–6	10 (45)
≥7	1 (5)
APACHE II score[13]	
≤5	3 (13)
5–10	10 (44)
11–15	8 (35)
16–20	1 (4)
≥21	1 (4)

Values in parentheses are percentages. * Patients staged at the time of admission or transfer to our hospital, not necessarily at time of onset of pancreatitis; † one patient unable to be adequately staged

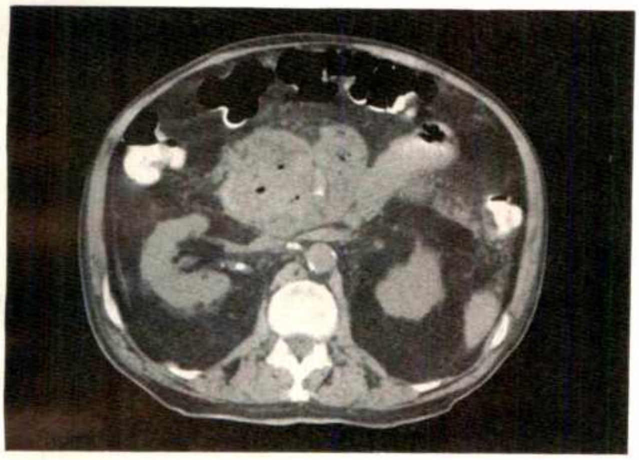

Figure 1 *Computed tomography showing extraluminal gas, diagnostic of pancreatic abscess*

induced in five, postoperative in four, related to endoscopic retrograde pancreatography in two, and was of indeterminate aetiology in 12; no patient had alcohol-induced pancreatitis which makes our series distinctly different from other reports.

Clinical characteristics

Twelve patients were admitted or transferred within 3 days of the onset of acute pancreatitis, five patients were transferred between 1 and 4 weeks after the onset, and six patients were managed elsewhere for more than 30 days before transfer. Because of incomplete or unconfirmable data from the referring hospitals, not all patients could be reliably scored at the onset of acute necrotizing pancreatitis. Therefore, all patients were scored by the criteria below at the time of admission to our medical centre.

Using the Ranson criteria[11], the majority of the patients (72 per cent) had six or less criteria, while using the Imrie criteria[12] all but one patient had less than seven criteria (*Table 1*). However, only 12 of 23 patients were seen at our institution at the onset of their pancreatitis, and the Ranson and Imrie criteria are most appropriate and predictive of severe pancreatitis when applied to the first 48 h after onset of pancreatitis. For these reasons and others[14], we also scored patients with the APACHE II classification[13]. Thirteen patients had 10 or fewer points, while nine had 11 to 20 points, and only one had greater than 21 points (*Table 1*).

Diagnosis of necrotizing pancreatitis

The diagnosis of necrotizing pancreatitis was made preoperatively in 22 of the 23 patients. Necrotizing pancreatitis was recognized preoperatively by a combination of clinical presentation and laboratory evaluation and by findings on CT. All had what appeared to be an enlarged pancreas on routine CT with peripancreatic fluid in 21 (95 per cent); three had well defined fluid collections. Sixteen patients had thickening of the anterior pararenal fascia, more frequently on the left. Only eight of the 18 patients (44 per cent) with either infected necrosis or pancreatic abscesses had extraluminal gas detected on CT.

Contrast-enhanced CT (Figures 1–3)

Intravenous contrast-enhanced CT scans were reviewed in 23 patients. Twenty-two (96 per cent) of 23 patients had definite pancreatic enlargement at CT. All of the patients had variable amounts of peripancreatic fluid; 19 (83 per cent) had large amounts, three (13 per cent) had moderate amounts, and one patient (4 per cent) had a small amount. Thirteen patients had an intravenous contrast-enhanced CT examination within 72 h of surgical confirmation of pancreatic or peripancreatic necrosis. Seven of these 13 patients (54 per cent) had a region(s) of absent pancreatic parenchymal enhancement which correlated with parenchymal necrosis documented either surgically or histologically. In all seven patients, the pancreatic body had absent enhancement. The entire pancreas did not enhance in one patient, and the head of the pancreas was non-enhancing in addition to the body in another two patients.

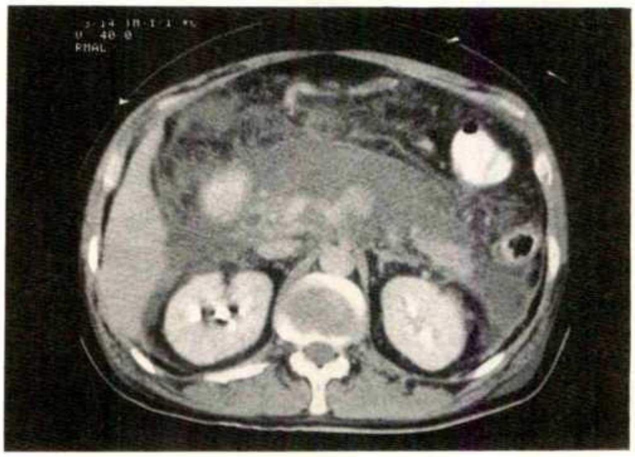

Figure 2 *Dynamic contrast-enhanced computed tomography demonstrating patchy areas of no pancreatic enhancement in head and body of pancreas in a severely toxic patient with non-infected pancreatic necrosis*

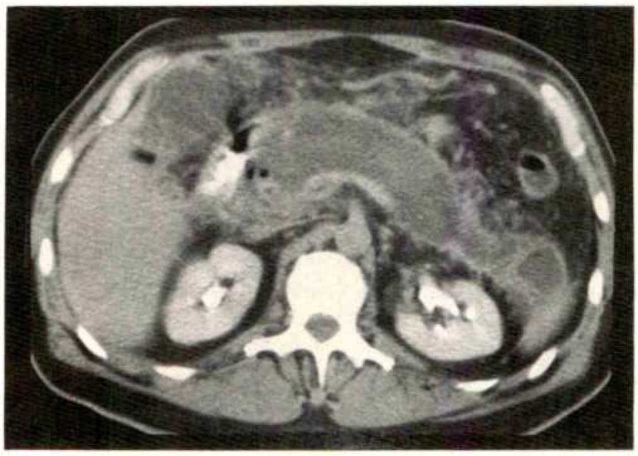

Figure 3 *Dynamic contrast-enhanced computed tomography demonstrating lack of pancreatic parenchymal enhancement throughout entire gland. At operation, this patient had isolated necrosis of the entire pancreas*

Table 2 *Necrotizing pancreatitis: other operative findings at initial exploration*

Findings	No. of patients
Pancreatic parenchymal necrosis	18 (78)
Entire gland (2 patients)	
Segmental areas entire gland (6 patients)	
Segmental areas body/tail (10 patients)	
Peripancreatic necrosis*	5 (22)
Perinephric/retroperitoneal paracolic necrosis	10 (43)
Right only (1 patient)	
Left only (2 patients)	
Bilateral (7 patients)	
Duodenal necrosis	1 (4)
Colonic necrosis	1 (4)

Values in parentheses are percentages. * No definite pancreatic parenchymal necrosis

The six patients with normal pancreatic enhancement had peripancreatic (five patients) or patchy pancreatic necrosis (one patient) without significant segmental regions of glandular destruction.

Percutaneous CT-guided needle aspiration was attempted in12 patients in order to diagnose infected necrosis or abscess. Cultures were negative in the two patients with non-infected necrosis and were positive in one of two patients with infected necrosis and six of seven patients with pancreatic abscess. The organisms grown from cultures obtained later at operation corresonded with the preoperative needle aspirations in each patient. Several patients underwent repeated needle aspirations during their initial non-operative course; positive cultures from the later aspirations were consistent with a deterioration in the patient's clinical course, thus necessitating operative intervention.

Indication for operation

Findings of extraluminal gas on CT (eight patients) or culture-positive CT-guided needle aspirations of peripancreatic fluid collections (seven patients) were absolute indications for operative intervention. The remaining patients were subjected to operative treatment because of a deteriorating clinical course of severe acute pancreatitis in the absence of other treatable complications (eight patients).

Operative findings/management

At the time of initial exploratory laparotomy (usually via a bilateral subcostal incision which we believe affords the best exposure), all but five patients had evidence of severe, pancreatic parenchymal necrosis (*Table 2*). The necrosis involved and was limited to the pancreas in two patients, each of whom underwent a 95 per cent pancreatectomy with the necrotic pancreas removed bluntly. In the remaining 16 patients, the necrosis was more patchy and segmental. Six underwent localized debridement/necrosectomy in portions of the head, body, and tail of the gland, while in ten patients, necrosectomy was required only in the body and tail. Every attempt was made to remove as much of the pancreatic and peripancreatic necrosis as was deemed safe. In three patients, the initial debridement involved extensive peripancreatic necrosis without any definite evidence of parenchymal necrosis. Two other patients had what the surgeon believed was pancreatic necrosis, and a distal pancreatectomy was performed; histopathological review of the specimen showed viable pancreatic parenchyma.

In addition to pancreatic and peripancreatic necrosis, the necrotizing process extended down the paracolic retroperitoneum in ten patients and required wide necrosectomy. The necrosis was bilateral in seven patients, and limited to the left side in two patients and to the right side in one patient. The left transverse colon and splenic flexure was involved with transmural infarction in one patient, necessitating colectomy and proximal diversion. In another patient, a 2 cm diameter area of the medial wall of the second portion of the duodenum was found to be necrotic during near total pancreatectomy and was managed by diverticulization of the duodenum 2 days later (stapling across the pylorus, tube choledochostomy, gastrojejunostomy, and local drainage).

After completing the initial necrosectomy, the peripancreatic area and paracolic retroperitoneal areas, if involved, were further debrided with the high pressure 'water pik' debrider-irrigation system (Surgilav, Model 201, Stryker Corp., Kalamazoo, Michigan, USA) and packed with gauze; the wound was then approximated, usually with the aid of a zipper[15]. Patients were returned to the operating room every other day until all grossly necrotic tissue was debrided, and the surgeon felt that the necrotizing process had ceased and as much devitalized tissue as possible was removed. Three patients underwent only the first necrosectomy, three required one reoperation, five required two and three reoperations, and seven underwent five or more reoperations. At the time of the final necrosectomy, attempts were made to close the abdominal fascia in a delayed primary fashion after leaving either multiple Penrose or soft, closed suction drains in the bed of the pancreas. This method of closure was possible in 14 patients. In the remaining nine patients, the wound was only able to be closed partially in four patients. In five patients, the pancreatic bed was 'marsupialized' either because of a severe complication or because tissue oedema prevented approximation of the fascial edges.

Bacteriology

Bacterial cultures obtained intraoperatively were negative in seven patients. Five of these patients had non-infected necrosis, but two patients who had obvious pancreatic abscesses had been placed on appropriate antibiotic coverage preoperatively after positive percutaneous needle aspirations. Gram negative organisms were recovered in 11 patients, Gram positive organisms in six, anaerobes in three, and yeast (*Candida* species) in four. Two patients had pure growths of yeast. Single organisms were obtained in 12 patients and multiple organisms in four.

Mortality and morbidity

Four patients died (17 per cent); three developed mutiple organ failure as a result of complications directly relating to the necrotizing pancreatitis, and one died of a pulmonary embolus just before discharge (*Table 3*). One death occurred in the five patients with non-infected necrosis, one death occurred in the three patients with infected necrosis, and two deaths occurred among the 15 patients with pancreatic abscess.

Significant hospital morbidity occurred in 12 patients (52 per cent). Controlled pancreaticocutaneous fistulae developed in six patients either via drain sites or through the marsupialized wound; all these patients had definite pancreatic

Table 3 *Necrotizing pancreatitis: postoperative hospital mortality and morbidity*

Morbidity	No. of patients
Death	4 (17)
Pancreatic fistula	6 (26)
Intra-abdominal abscess	1 (4)
Percutaneous drainage (1 patient)	
Reoperation (0 patients)	
Haemorrhage/reoperation	6 (26)
Colonic fistula/necrosis	5 (22)
Requiring ileostomy/diversion	2 (9)
Small bowel fistula	3 (13)
Gastric fistula	2 (9)

Values in parentheses are percentages

Table 4 *Necrotizing pancreatitis: long term morbidity after discharge from hospital* (n = *19 patients*)

Morbidity	No. of patients
Pancreatic fistula	5 (26)
Spontaneous closure	2
Operative closure	3
Intra-abdominal abscess	2 (11)
Percutaneous drainage	1
Reoperation	1
Pancreatic insufficiency	7 (37)
Exocrine	6
Endocrine	3*
Pseudocyst	0
Recurrent pancreatitis	2 (11)
Small bowel fistula	1 (6)

Values in parentheses are percentages. * Insulin-dependent in two patients

parenchymal necrosis. Recurrent intra-abdominal abscess in the right paracolic gutter occurred in only one patient (4 per cent) and was treated successfully by percutaneous drainage. Severe haemorrhage requiring reoperation occurred in six patients with involvement of splenic or pancreatic vessels (two patients), portal vein (one patient), and middle colic vessels (three patients). Colonic necrosis or fistulae developed in five patients. One patient had transmural necrosis at initial necrosectomy and was treated by subtotal colectomy and ileostomy. Necrosis of the transverse colon was noted at the time of repeat necrosectomy/debridement in another patient and was treated by proximal loop ileostomy. Three other patients developed transient colonic fistulae out of the wound; all closed spontaneously. Small bowel and gastric fistulae developed in three and two patients, respectively. One small bowel fistula persisted until the time of death 77 days after operation in one patient; the remainder closed spontaneously before discharge. Median duration of hospital stay was 50 days (range, 13–270 days).

Long-term morbidity was also significant (*Table 4*). Of the five patients discharged with a pancreaticocutaneous fistula, two closed spontaneously, but three eventually required operative intervention with drainage of a persistent fistula into a Roux-en-Y jejunal limb. Late intra-abdominal abscess occurred in two patients (>3 months after discharge), one each treated by operative or percutaneous drainage. Pancreatic insufficiency developed in seven patients, necessitating oral pancreatic enzyme replacement in six, insulin administration in two, and an oral hypoglycaemic agent in one. No patient developed a pancreatic pseudocyst, although two patients experienced recurrent pancreatitis. One patient developed a late small bowel fistula that closed spontaneously.

Correlation of morbidity with preoperative staging

The best predictors of postoperative morbidity were the Ranson and Imrie scores; both were correlated with the postoperative development of some clinically significant complication (Ranson, $P<0{\cdot}06$; Imrie $P<0{\cdot}05$). The APACHE-II scoring classification, as we used it, was not correlated with development of postoperative morbidity/mortality ($P=0{\cdot}36$).

Discussion

The management of necrotizing pancreatitis has evolved dramatically over the last two decades[16]. Historically, wide peripancreatic drainage was associated with a high incidence of recurrent intra-abdominal sepsis and multiple organ failure[17–20]. With the addition of pancreatic necrosectomy/debridement, overall morbidity and mortality has improved markedly[2,9,21–26]. Our previously described technique of controlled open lesser sac drainage[9] has further evolved in our hands preferably to include planned repeated necrosectomy and debridement with eventual delayed primary fascial closure over drains whenever possible. This technique of wound management avoids the large, open wound necessitated by the various techniques of marsupialization[18,21–23] and allows for pancreatic ductal leaks to be better contained as controlled external fistulae. Moreover, the repeated operative necrosectomy and debridement until the necrotizing process has stopped and all devitalized tissue is excised minimizes the incidence of recurrent intra-abdominal sepsis.

The major problem with operative management of necrotizing pancreatitis in the past has been recurrent intra-abdominal sepsis requiring reoperation, undoubtedly related to persistent pancreatic and peripancreatic infected necrosis not effectively evacuated with drains[10,17–20]. In attempts to encourage the ongoing evacuation of both the necrotizing process and the leakage of pancreatic secretion, multiple techniques have been suggested. Formal pancreatic resection was associated with an inordinate mortality rate[27–29]. More recent techniques have included open marsupialization of the pancreatic bed by Stone, Bradley and others[9,18,21–23], continuous postoperative peripancreatic irrigation by Beger and others[2,24,25], and wide peripancreatic drainage as advocated by Warshaw and Gongliang[26]. All the above techniques included formal necrosectomy followed by various attempts to maximize and control drainage, and each method improved the operative mortality rate to ≤20 per cent. However, recurrent intra-abdominal sepsis requiring redrainage still occurred in a significant number of patients. We believe that recurrent sepsis arises from areas of persistent necrosis that escaped debridement either because the area was not operatively exposed or because the necrotizing process continued after the initial necrosectomy and debridement. Our recent experience with repeated operative necrosectomy and debridement has convinced us that repeated reoperative inspection of the entire pancreatic and peripancreatic bed on an every other day basis is very important. Not uncommonly we have found areas of necrosis that were judged viable initially but evolved to unequivocal necrosis during the interval between repeated operative debridement. We continue to use an approach of planned operative re-exploration to debride the pancreatic bed and retroperitoneal paracolic gutters using both blunt necrosectomy and the 'water pik' debrider–irrigator system until we are convinced that the necrotizing process has stopped and that all non-viable tissue has been excised. In our most recent experience, 17 of 23 patients (74 per cent) required more than two re-explorations for complete necrosectomy and debridement. With this approach, only one of 23 patients (4 per cent) developed a recurrent intra-abdominal abscess before discharge which was drained percutaneously.

Because of the need for repeated re-explorations, the use of 'zipper' reapproximation of the wound edges[15] speeds the operative procedures and minimizes fluid losses between re-explorations; moreover, by both keeping the wound edges reapproximated and the intra-abdominal contents within the abdominal domain, eventual delayed primary fascial closure is facilitated. Closure of the wound also prevents the desiccation of tissues that can occur with open wound management with marsupialization and may minimize development of contact-induced enteric fistulae. Wide peripancreatic placement of soft drains at the time of fascial closure is also of crucial importance because of the high incidence of pancreatic fistula (26 per cent in our series) and the need for evacuation of ongoing exudate from areas of infected necrosis. We have tended to avoid the large sump drains except in selected cases because invariably they are stiff and can erode adjacent structures (bowel, blood vessels).

Development of gastrointestinal fistulae further confounds the treatment of necrotizing pancreatitis. The pathogenesis is multifactorial. The necrotizing process itself can extend into the peripancreatic structures, causing local vascular thrombosis and resultant ischaemia. This problem is especially relevant to the transverse colon[30] because the necrotizing process is often intimately involved with the middle colic vessels. In our study, colonic necrosis and/or fistula occurred in five patients (22 per cent). The duodenum may also be affected as seen in one of our patients. Fistulae may in part be iatrogenic. With marsupialization of the pancreatic bed through open packing, recurrent topical trauma to the serosal surface of the bowel can lead to a fistula. Allegedly, application of a non-adherent gauze (Adaptic, Johnson & Johnson, New Brunswick, New Jersey, USA) to the bowel surfaces may minimize this possibility[22]. Provided there is no distal obstruction and the area is well drained, most fistulae will close. Occasionally, large colonic fistulae or areas of extensive transmural infarction may require proximal diversion (loop ileostomy) or colectomy.

Haemorrhage is another major complication that occurred in six patients (26 per cent). Intraoperative bleeding is a very real concern during the necrosectomy. Sharp debridement is discouraged, and efforts should be made to preserve any vessels in the pancreatic bed. Haemorrhage in our patients included both arterial and venous sources. With necrosectomy of the body and tail of the pancreas, the splenic artery and vein may be fully exposed. Similarly, with involvement of the transverse mesocolon in the necrotizing process, the middle colic vessels are at risk for injury. Just as with the development of gastrointestinal fistulae, haemorrhage in the postoperative period may ensue from a direct injury to the vessel wall from the necrotizing process or from drains or open packing. Although we believe that avoidance of stiff sump drains and avoidance of marsupialization which necessitates gauze packing of the pancreatic bed should minimize this complication, haemorrhage remains a serious problem, and haemodynamically significant bleeding necessitates immediate intervention, either with angiographic embolization when possible[26] or with immediate reoperation.

A recent advance in the recognition of necrotizing pancreatitis has been the use of dynamic, contrast-enhanced CT imaging in conjunction with percutaneous aspiration of the pancreatic bed. With the contrast-enhanced CT technique, pancreatic parenchymal necrosis can now be differentiated from acute (viable) pancreatitis with an intense peripancreatic inflammatory reaction. Although the therapeutic application of this diagnostic method in determining the need for operative treatment is still controversial, it may help in prognosis and staging of the patient with severe acute pancreatitis. Moreover, the presence of pancreatic necrosis can be used as an indication for CT-guided percutaneous needle aspiration of questionable areas looking specifically for infected necrosis[31] – an absolute indication for operative treatment. These techniques proved useful in our recent experience. The dynamic contrast-enhanced CT may aid the surgeon in determining the extent of necrosectomy, especially in the head and uncinate process once the decision to operate has been made based on other factors described above. Whether greater than 50 per cent necrosis of the pancreas alone, without documented infection, is in itself an indication for operative intervention remains unclear[32], because we have noticed that selected patients with extensive pancreatic parenchymal necrosis managed without operative treatment have recovered.

The indications for operative treatment of necrotizing pancreatitis are still not completely defined. Non-controversial indications include the presence of extraluminal gas on CT or a culture-positive needle aspiration of peripancreatic fluid which are pathognomonic of peripancreatic sepsis and require operative treatment. More controversial indications, however, include the decision to intervene in patients with a normally perfused pancreas on contrast-enhanced CT who exhibit a deteriorization in clinical course without another identified complication. These patients may have infected peripancreatic necrosis in the absence of parenchymal necrosis; our experience and that of others[31,33] has shown that repeated CT-guided needle aspirations can prove very helpful and specific in documenting infection in these patients. An equally controversial indication for operative treatment includes patients early in their clinical course (<2 weeks) with severe pancreatic parenchymal necrosis but without documented infection who exhibit a relentless downhill course believed related to the necrotizing process. Obviously, the decision to intervene is a difficult one and requires clinical judgement with a thorough consideration of the clinical situation and other non-operative means of supportive care.

Nutritional support is imperative in these patients and may represent at least one factor intimately involved in the improved operative results in necrotizing pancreatitis. All these patients were supported with total parenteral nutrition in the perioperative period. Thereafter, many were converted to enteral nutritional support, either via a gastrostomy or feeding jejunostomy placed at the time of wound closure or more recently via needle catheter jejunostomy. The latter technique was used in 11 patients and may afford the best alternative for enteral feeding with the least risk[34].

Finally, one point that has not been previously emphasized is the significant long term morbidity that occurs among surviving patients with severe necrotizing pancreatitis. In addition to pancreatocutaneous fistulae, gastrointestinal fistulae, and occasional recurrent intra-abdominal abscesses, pancreatic insufficiency is a common sequela. Six of the 19 survivors in this series required oral pancreatic enzyme replacement, two required insulin, and one required an oral hypoglycaemic agent. Although others have been surprised by the frequently unremarkable endoscopic pancreatograms in this group of patients following recovery[35], such patients may well have had peripancreatic necrosis but viable pancreatic parenchyma.

In summary, necrotizing pancreatitis is a serious disease. We believe that the technique of repeated, operative necrosectomy/debridement followed by delayed primary fascial closure over drains minimizes the incidence of recurrent intra-abdominal abscess related to persistent necrosis and undrained fluid. Within this group, mortality was high (17 per cent), and long term related morbidity is significant.

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References

1. Bittner R, Block S, Buchler M, Beger HG. Pancreatic abscess and infected pancreatic necrosis: different local septic complications in acute pancreatitis. *Dig Dis Sci* 1987; **32**: 1082–7.
2. Beger HG, Buchler M, Bittner R, Block S, Nevalainen T, Roscher R. Necrosectomy and postoperative local lavage in necrotizing pancreatitis. *Br J Surg* 1988; **75**: 207–12.
3. Frey CF, Bradley EL, Beger HG. Progress in acute pancreatitis. *Surg Gynecol Obstet* 1988; **167**: 282–6.
4. Kivisaari L, Somer K, Standertskjold-Nordenstam C-G, Schroder T, Kivilaakso E, Lempinen M. Early detection of acute, fulminant pancreatitis by contrast-enhanced computed tomography. *Scand J Gastroenterol* 1983; **18**: 39–41.
5. Block S, Maier W, Bittner R, Buchler M, Malfertheiner P, Beger HG. Identification of pancreas necrosis in severe acute pancreatitis: imaging procedures versus clinical staging. *Gut* 1986; **27**: 1035–42.
6. London NJM, Neoptolemos JP, Lavelle J, Bailey I, James D. Serial computed tomography scanning in acute pancreatitis: a prospective study. *Gut* 1989; **30**: 397–403.
7. Ranson JHC, Balthazar E, Caccavale R, Cooper M. Computed tomography and the prediction of pancreatic abscess in acute pancreatitis. *Ann Surg* 1985; **201**: 656–65.
8. White EM, Wittenberg J, Mueller PR *et al.* Pancreatic necrosis: CT manifestations. *Radiology* 1986; **158**: 343–6.
9. Pemberton JH, Becker JM, Dozois RR, Nagorney DM,

Ilstrup D, ReMine WH. Controlled open lesser sac drainage for pancreatic abscess. *Ann Surg* 1986; **203**: 600–4.
10. Warshaw Al. Pancreatic abscesses. *New Engl J Med* 1972; **287**: 1234–6.
11. Ranson JHC, Ritkind KM, Rases DF, Fink SD, Eng K, Spencer FC. Prognostic signs and the role of operative management in acute pancreatitis. *Surg Gynecol Obstet* 1974; **139**: 69–81.
12. Osborne DH, Imrie CW, Carter DC. Biliary surgery in the same admission for gallstone-associated acute pancreatitis. *Br J Surg* 1981; **68**: 758–61.
13. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; **13**: 818–29.
14. Larvin M, McMahon MJ. APACHE-II score for assessment and maintaining of acute pancreatitis. *Lancet* 1989; **ii**: 201–4.
15. Leguit P Jr. Zip-closure of the abdomen. *Neth J Surg* 1982; **34**: 40–1.
16. Poston GJ, Williamson RCN. Surgical management of acute pancreatitis. *Br J Surg* 1990; **77**: 5–12.
17. Aranha GV, Prinz RA, Greenlee HB. Pancreatic abscess: an unresolved surgical problem. *Am J Surg* 1982; **144**: 534–8.
18. Bolooki H, Jaffe B, Gleidman ML. Pancreatic abscesses and lesser omental sac collections. *Surg Gynecol Obstet* 1968; **126**: 1301–8.
19. Frey CF, Lindenauer SM, Miller TA. Pancreatic abscess. *Surg Gynecol Obstet* 1979; **149**: 722–6.
20. Fink AS, Hiatt JR, Pitt HA *et al.* Indolent presentation of pancreatic abscess: experience with 100 cases. *Arch Surg* 1988; **123**: 1067–72.
21. Davidson ED, Bradley EL III. 'Marsupialization' in the treatment of pancreatic abscess. *Surgery* 1981; **89**: 252–6.
22. Bradley EL. Management of infected pancreatic necrosis by open drainage. *Ann Surg* 1987; **206**: 542–50.
23. Stone HH, Strom PR, Mullins RJ. Pancreatic abscess management by subtotal resection and packing. *World J Surg* 1984; **8**: 340–5.
24. Teerenhovi O, Nordback I, Eskola J. High volume lesser sac lavage in acute necrotizing pancreatitis. *Br J Surg* 1989; **76**: 370–3.
25. Larvin M, Chalmers AG, Robinson PJ, McMahon MJ. Debridement and closed cavity irrigation for the treatment of pancreatic necrosis. *Br J Surg* 1989; **76**: 465–71.
26. Warshaw AL, Gongliang J. Improved survival in 45 patients with pancreatic abscess. *Ann Surg* 1985; **202**: 408–15.
27. Edelman G, Boutelier P. Le traitement des pancreatites aigues necrosantes par l'ablation chirurgicale precoce des portions necroses. *Chirurgie* 1974; **100**: 155–67.
28. Alexandre JH, Guerreri MT. Role of total pancreatectomy in the treatment of necrotizing pancreatitis. *World J Surg* 1981; **5**: 369–77.
29. Aldridge MC, Ornstein M, Glazer G, Dudley HAF. Pancreatic resection for severe acute pancreatitis. *Br J Surg* 1985; **72**: 796–800.
30. Aldridge MC, Francis ND, Glazer G, Dudley HAF. Colonic complications of severe acute pancreatitis. *Br J Surg* 1989; **76**: 362–7.
31. Hill MC, Dach JL, Barken J, Isikoff MB, Morse B. The role of percutaneous aspiration in the diagnosis of pancreatic abscess. *Am J Radiol* 1983; **141**: 1035–8.
32. Bradley EL III, Murphy F, Ferguson C. Prediction of pancreatic necrosis by dynamic pancreatography. *Ann Surg* 1989; **210**: 495–504.
33. Banks PA, Gerzof SG, Chong FK *et al.* Bacteriological status of necrotic tissue in necrotizing pancreatitis. *Pancreas* 1990; **5**: 330–3.
34. Sarr MG, Mayo S. Needle catheter jejunostomy: an unappreciated and misunderstood advance in the care of patients after major abdominal operations. *Mayo Clin Proc* 1988; **63**: 565–72.
35. Howard JM, Wagner SM. Pancreatography after recovery from massive pancreatic necrosis. *Ann Surg* 1989; **209**: 31–5.

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Treatment of oesophageal perforation: a multivariate analysis

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Perforation of the oesophagus was retrospectively analysed in 59 patients. Cause and extent of perforation, localization, quality of the oesophageal wall and therapeutic modes were subjected to univariate analysis. The perforations of the intrathoracic oesophagus (39) were also subjected to multivariate analysis. Perforation of the cervical oesophagus is seldom lethal and can be adequately treated conservatively in the majority of cases. Perforations of the intrathoracic oesophagus can be divided into two groups, with or without simultaneous perforation of the parietal pleura. The optimal treatment for the group with pleural perforation seems to be resection of the oesophagus and secondary reconstruction, although primary closure is indicated in selected early cases. Perforations of the intrathoracic oesophagus confined to the mediastinum can be adequately treated conservatively in most patients. Perforation of the intra-abdominal oesophagus should be treated like any other intra-abdominal visceral perforation, by closure or diversion, even if this results in resection of the oesophagus.

Perforation of the oesophagus is a life-threatening condition regardless of the therapeutic approach. The majority of perforations are iatrogenic by instrumentation. Infrequently perforations are due to external violence or ingestion of a foreign body, or are spontaneous. The prognosis will largely depend on cause and site of perforation, the underlying disease, the interval and the condition of the patient. Whereas conservative treatment will suffice for some cases, oesophageal resection seems indicated in others. To establish the optimal mode of treatment of the different forms of oesophageal perforation, 59 patients treated for a perforation of the oesophagus were analysed.

Patients and methods

Between 1972 and 1989, 59 patients were treated for a perforation of the oesophagus (*Table 1*). Patients with anastomotic fistulae were excluded from this study. There were 20 women and 39 men with a mean age of 57 years (range 14–81 years). The location of the perforation was the cervical part of the oesophagus in 13 patients, the intrathoracic part in 39 patients and the abdominal part in seven patients. Instrumental manipulation was the most common cause of perforation ($n=32$). Other causes were operation ($n=7$), ingestion of a foreign body ($n=7$) or penetrating trauma ($n=5$). Eight perforations occurred spontaneously. The overall in-hospital mortality rate was 29 per cent.

Statistical analysis

Patients with cervical, intrathoracic and intra-abdominal perforations were studied as three different groups. Within each group, the observed outcome was univariately related to the treatment chosen and a set of clinical variables: age (dichotomized at 50 years), sex, time elapsed between perforation and start of treatment (dichotomized at 24 h), integrity of the parietal pleura (yes/no), cause of perforation (instrumental manipulation, ingestion of foreign body, upper abdominal surgery, spontaneous, external violence) and quality of the oesophageal wall (normal, benign diseased, malignant diseased).

Making any conclusions on the mortality rates observed in the treatment groups based on a univariate analysis is not straightforward, because patients in each subgroup could have differed with regard to relevant clinical variables. The choice of therapy could have been guided by these differences, which might account for the differences in mortality rate in a comparison of treatments. Such a selection bias was very likely to occur, and cannot be eliminated *post hoc*. To gain a better description of the relative contribution of treatment choice to observed survival, the relation between treatment, clinical variables and observed outcome was evaluated in a multivariate model. Because of the number of patients in each subgroup, such an analysis was performed only in the intrathoracic group. Even in this group, the number of patients is rather small, which prevents firm conclusions.

In a logistic model, the natural logarithm of the mortality odds is linearly related to a weighted sum of the treatment chosen and clinical variables. An example is:

$$\frac{p(\text{mort}|\text{treatment}, X_1, X_2)}{1-p(\text{mort}|\text{treatment}, X_1, X_2)} = \beta_1 + \beta_2\ \text{treatment} + \beta_3 X_1 + \beta_4 X_2$$

where $p(\text{mort}|\text{treatment}, X_1, X_2)$ stands for the probability of death in the subgroup of patients sharing a particular treatment (the variable treatment) and having in common values of clinical variables, represented by the variables X_1, X_2. Values of the coefficients β_1, β_2, β_3 and β_4 are estimated by the technique of maximum likelihood. The coefficient β_1 is commonly called the intercept, as in ordinary linear regression. Several logistic regression models were fitted. The first model contained only the treatment variable. This variable has three values, but we replaced it with two indicator variables: 'resected' (yes/no) and 'local repair' (yes/no). Oesophageal resection is represented as resected–yes, local repair–no; local repair as resected–no, local repair–yes; and conservative treatment as resected–no, local repair–no. In additional models, clinical variables were included if they led to a substantial improvement of the model's descriptive quality. This was assessed using likelihood ratio tests, as was the contribution of the two treatment indicator variables.

Results

The results are summarized in *Table 1*.

Perforation of the cervical oesophagus (n = *13*)

Cause of the perforation was ingestion of a foreign body in four patients and instrumentation in three patients. One accidental perforation occurred during thyroidectomy. Five perforations were caused by external penetrating trauma. In all cases except one, the diagnosis was made within 24 h. In one patient the parietal pleura was opened, resulting in a pneumothorax.

In ten patients the treatment was conservative, with drainage of a cervical abscess in one. Three patients were treated with primary closure: the patient with perforation during thyroidectomy, one patient with transection of the trachea and oesophagus during an attempted suicide, and one patient with a knife perforation. Neither in the conservatively treated group nor in the three patients treated with primary closure were there any deaths.

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Table 1 *Number of patients and observed mortality rates in total and according to location of perforation*

Variable	Total			Intrathoracic			Intra-abdominal			Cervical*
	n	Deaths	%	*n*	Deaths	%	*n*	Deaths	%	*n*
	59	17	29	39	14	36	7	3	43	13
Therapy										
Conservative	27	9	33	16	8	50	1	1	100	10
Local repair	13	4	31	7	3	43	3	1	33	3
Resected	19	4	21	16	3	19	3	1	33	0
Interval										
≤24 h	39	11	28	24	10	42	3	1	33	12
>24 h	20	6	30	15	4	27	4	2	50	1
Cause										
Instrumental	32	11	34	27	10	37	2	1	50	3
Ingestion	7	1	14	3	1	33	0	–	–	4
Upper abdominal surgery	7	2	29	1	0	0	5	2	40	1
Spontaneous	8	3	38	8	3	38	0	–	–	0
External violence	5	0	0	0	–	–	0	–	–	5
Parietal pleura										
Intact	29	5	17	12	2	17	5	3	60	12
Open	30	12	40	27	12	44	2	0	0	1
Sex										
Male	39	13	33	26	12	46	5	1	20	8
Female	20	4	20	13	2	15	2	2	100	5
Age										
≤50 years	17	3	18	10	2	20	2	1	50	5
>50 years	42	14	33	29	12	41	5	2	40	8
Oesophageal wall										
Normal	26	5	19	12	4	33	2	1	50	12
Diseased (benign)	22	6	27	17	5	29	4	1	25	1
Diseased (malignant)	11	6	55	10	5	50	1	1	100	0

*There were no deaths in the group with cervical perforation

Perforation of the intrathoracic oesophagus (n = *39*)

Univariate analysis. In the group of 39 patients with perforation of the intrathoracic oesophagus there existed a marked difference in mortality rate between men (46 per cent) and women (15 per cent) (Fisher's exact test $P = 0{\cdot}008$). This difference was regardless of age, interval, cause, pathology of the oesophageal wall or integrity of the parietal pleura. For patients of 50 years or younger the mortality rate was lower. The majority of the intrathoracic perforations were caused by instrumental manipulation ($n = 27$). All spontaneous perforations were intrathoracic ($n = 8$). Ingestion of a foreign body ($n = 3$) and operation ($n = 1$) accounted for the other perforations. The cause of the perforation had little influence on mortality rate. Regarding the quality of the oesophagus, there was a higher mortality rate (50 per cent) in patients with a malignant perforation. Patients with an interval of 24 h or less between perforation and start of treatment had a higher mortality rate (42 per cent) than patients with a longer interval (27 per cent). This difference was not significant. A marked difference in mortality rate exists between patients with a perforation confined to the mediastinum (17 per cent) and patients with a simultaneous perforation of the parietal pleura (44 per cent). Conservative treatment or drainage of the thoracic cavity only ($n = 16$) resulted in a mortality rate of 50 per cent. Three of seven patients with a local repair, i.e. primary closure of the perforation, and three of 16 patients with an oesophageal resection died.

Multivariate analysis. Table 2 contains the logistic models that were fitted in the intrathoracic group, with the corresponding values of −2 log likelihood, variables included, estimated coefficients, and their estimated standard error.

The intercept in each model indicates the (estimated) log odds for mortality, other variables in the model excluded. For example, in model 1, the intercept stands for the estimated log mortality odds in the group of conservatively treated patients (no resection, no local repair). For the remaining groups, one adds the corresponding coefficient to arrive at the log odds for mortality. In model 1, for example, the (estimated) log odds for mortality in the group of resected patients equals $0 - 1{\cdot}466$. Similarly, the (estimated) log odds for mortality in the group of patients treated with local repair equals $0 - 0{\cdot}288$.

Model 1 contains the two treatment indicator variables only. The integrity of the parietal pleura was the only clinical variable that led to a model with a substantially better descriptive quality (model 2 *versus* model 1; $P = 0{\cdot}002$).

The omission of the indicator variable 'local repair' (model 3) did not lead to a substantially worse descriptive quality ($P = 0{\cdot}193$). Yet a further removal of either the other indicator variable or the variable 'pleura intact' did lead to deterioration of the descriptive quality.

Table 2 *Mortality in 39 patients with a perforation of the intrathoracic oesophagus: logistic regression models*

Model	Variable	Estimated coefficient	Standard error	−2 log likelihood
Null model				50·920
	Intercept	0·580	0·334	
Model 1				47·184
	Intercept	0·000	0·500	
	Resected	−1·466	0·813	
	Local repair	−0·288	0·913	
Model 2				37·277
	Intercept	1·928	1·073	
	Resected	−3·318	1·248	
	Local repair	−1·606	1·328	
	Pleura intact	−3·253	1·281	
Model 3				38·975
	Intercept	1·106	0·665	
	Resected	−2·500	0·923	
	Pleura intact	−2·621	1·021	

Perforations of the intra-abdominal oesophagus (n = 7)

Two intra-abdominal perforations occurred during endo-oesophageal instrumentation and five during operation. Only one patient had a malignancy. Four patients had oesophagitis and two had a normal oesophagus. The two perforations due to instrumentation also had perforation of the parietal pleura. In the five other cases the parietal pleura was intact. Three perforations were diagnosed and treated during the primary operation; in four patients more than 24 h were needed to establish the diagnosis.

Therapy was conservative in one patient. The perforation was closed and buttressed with an omental pedicle in three. Three patients had a subtotal oesophagectomy with oesophago-cutaneostomy and gastrostomy. This treatment could not prevent three deaths, one in each group of the three different treatment modes (*Table 1*).

Discussion

Unless perforation of the oesophagus is localized in the cervical part, it is a potentially life-threatening condition with a mortality rate between 15 and 30 per cent[1–3]. According to the literature different clinical variables such as cause of perforation, localizaton, time interval, condition of the oesophagus and simultaneous perforation of the parietal pleura are related to survival. Perforation is iatrogenic in more than half the cases[4]. Endoscopy with a rigid scope is associated with a perforation rate of 0·11–0·4 per cent[5,6]. With the introduction of the flexible instrument the perforation rate has decreased to 0·03 per cent, but a higher rate is reported after more extensive manipulations such as dilatation (0·25 per cent) and intubation (7·9 per cent)[7,8]. Pneumatic dilatation of achalasia is associated with a perforation rate of about 4 per cent[9,10]. In the present series 54 per cent of the perforations were caused by instrumental manipulation, resulting in a mortality rate of 34 per cent. Of the seven patients with perforation due to ingestion of a foreign body, one died from extensive mediastinal abscesses 1 year after removal of a fishbone. Spontaneous rupture of the oesophagus is related to a high mortality rate and radical surgery is advocated[11,12]. The mortality rate after spontaneous rupture in the present series was 38 per cent even after a radical surgical approach. Early recognition of the perforation is regarded as all-important and a 3–5-fold increase in mortality rate is reported[13,14] after delay of more than 24 h. However, in the present series no such difference in overall mortality rate in patients treated within or after 24 h was found.

Perforation of the cervical oesophagus has a good prognosis. Closure may offer no better results than simple drainage alone[15]. In this series no patient died after perforation of the cervical oesophagus. Conservative treatment with drainage only was successful in ten patients. In only three cases of total or subtotal oesophageal transection was primary closure performed. All 13 patients survived regardless of the chosen therapy. This may be an indication that the choice of therapy is not an important factor in survival after perforation of the cervical oesophagus.

Perforation of the intrathoracic oesophagus is more difficult to manage. Controversy exists regarding operative *versus* non-operative treatment. Guidelines were given[16] after the first successful response to conservative treatment[17]. Intramural perforations are rare and best treated conservatively[11], as are perforations confined to the mediastinum[18].

To negate the effect of patient selection and to establish the contribution of each of the clinical and therapeutic variables in reduction of mortality rate, logistic regression models were fitted. Of the clinical variables only the integrity of the parietal pleura had a significant positive influence on mortality rate. Regarding the therapeutic modes, the variable 'resection of the oesophagus *versus* all other forms of therapy' accounted for a significant difference in favour of resection. The overall mortality rate was not influenced by the time lag between perforation and therapy of choice in patients with a delay of days and/or weeks, and the survival was slightly but not significantly better after a delay of > 24 h in patients with an intrathoracic perforation. This may be due to small numbers, but another possibility is our aggressive therapeutic approach in patients with simultaneous perforation of the parietal pleura, and in 'late' cases[19,20].

Perforations of the intra-abdominal part of the oesophagus in this series were all accidental. The majority occurred during operation. One patient had a carcinoma of the oesophagus. During intubation the pleura as well as the peritoneum was perforated. This patient was the only one managed conservatively and he died shortly afterwards. The other perforations were treated by local repair. Fundoplication in three cases and resection in the remainder.

The retrospective nature of the study design and the small numbers in this series do not allow firm recommendations on how patients with a perforation of the oesophagus should be treated. Yet we feel that there are grounds for the following advice. For perforation of the cervical oesophagus a conservative approach can be recommended in the majority of cases. For perforation of the intrathoracic oesophagus there is a place for conservative treatment, but only for those perforations confined to the mediastinum. Once the parietal pleura is perforated, resection of the oesophagus seems to be the therapy of choice. Perforation of the intra-abdominal oesophagus may be treated like any other free intra-abdominal perforation.

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References

1. Ajalat GM, Mulder DG. Esophageal perforations. *Arch Surg* 1984; **119**: 1318–20.
2. Skinner DB, Little AG, DeMeester TR. Management of esophageal perforation. *Am J Surg* 1980; **139**: 760–4.
3. Wilde PH, Mullany CJ. Oesophageal perforation: a review of 37 cases. *Aust NZ J Surg* 1987; **57**: 743–7.
4. Bladergroen MR, Lowe JE, Postlethwait RW. Diagnosis and recommended management of esophageal perforation and rupture. *Ann Thorac Surg* 1986; **42**: 235–9.
5. Katz D. Morbidity and mortality in standard and flexible gastrointestinal endoscopy. *Gastrointest Endosc* 1967; **14**: 134–7.
6. Wychulis AR, Fontana RS, Payne WS. Instrumental perforations of the esophagus. *Dis Chest* 1969; **55**: 184–9.
7. Dawson J, Cockel R. Oesophageal perforation at fibreoptic gastroscopy. *Br Med J* 1981; **283**: 583.
8. Silvis SE, Nebel O, Rogers G *et al.* Endoscopic complications: results of the 1974 American Society of Gastrointestinal Endoscopy Survey. *JAMA* 1976; **235**: 928–35.
9. Michel L, Grillo HC, Malt RA. Esophageal perforation. *Ann Thorac Surg* 1982; **33**: 203–10.
10. Slater G, Sicular AA. Esophageal perforations after forceful dilatation in achalasia. *Ann Surg* 1982; **195**: 186–8.
11. Berliner LB, Redmond P, Pacnter HL. Spontaneous intramural perforation of the esophagus; case report and review of the literature. *Am J Gastroenterol* 1982; **77**: 355–7.
12. Petterson G, Larsson S, Gatzinsky P, Sudow G. Differentiated treatment of intrathoracic oesophageal perforation. *Scand J Thorac Cardiovasc Surg* 1981; **15**: 321–4.
13. Sawyers JL, Lane CE, Foster JH, Daniel RA. Esophageal perforation. *Arch Surg* 1975; **110**: 233–8.
14. Lyons WS, Serementir MG, deGuzman VC, Peabody JW. Rupture and perforation of the esophagus: the case for conservative supportive management. *Ann Thorac Surg* 1978; **25**: 346–50.
15. Brewer LA, Carter R, Mulder GA, Stiles QR. Options in the management of perforations of the esophagus. *Am J Surg* 1986; **152**: 62–9.
16. Cameron JC, Keiffer RF, Hendrix TR *et al.* Selective nonoperative management of contained intrathoracic esophageal disruptions. *Ann Thorac Surg* 1978; **27**: 404–8.

17. Mengoli LR, Klassen KP. Conservative management of esophageal perforation. *Arch Surg* 1965; **91**: 238–40.
18. Wesdorp ICE, Bartelsman JFWM, Huibregtse K, Den Hartog Jager FCA, Tytgat GN. Treatment of instrumental oesophageal perforation. *Gut* 1984; **25**: 398–404.
19. DeMeester TR. Perforation of the esophagus. *Ann Thorac Surg* 1986; **42**: 231–2.
20. Flynn AE, Verrier ED, Way LW, Thomas AN, Pellegrini CA. Esophageal perforation. *Arch Surg* 1989; **124**: 1211–15.

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Case report

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Toxic shock syndrome following insertion of breast prostheses

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Toxic shock syndrome (TSS) was first described in 1978[1]. During an epidemic of TSS in 1980 a link with the use of vaginal tampons was noted and toxin-producing *Staphylococcus aureus* was implicated as the causative agent.

The annual incidence of TSS associated with menstruation is 0·7 per 100 000 women. At least 15 per cent of TSS is not related to menstruation and may be caused by nosocomial infections.

A patient with TSS caused by infected breast prostheses is presented. Seven additional cases[2–7] are described in the literature.

Case report

A previously healthy 27-year-old woman had bilateral, inframammary, subglandular placement of silicone breast prostheses for cosmetic reasons. She developed fever and myalgia 12 h later, and 30 h after operation she developed vomiting, watery diarrhoea, sore throat and orthostatic dizziness.

On the fourth day after operation she was somnolent and confused, with hyperventilation, and had a temperature of 39·3°C. She was dehydrated with a blood pressure of 70/40 mmHg, low central venous pressure and a urine production rate of 10 ml/h. She had generalized erythema and hyperaemia of conjunctiva and oropharynx. A drop of pus was expressed from the right breast wound.

Investigations revealed features compatible with disseminated intravascular coagulopathy, adult respiratory distress syndrome, rhabdomyolysis and renal failure (acute tubulointerstitial nephropathy).

The patient had no vaginal discharge, did not use tampons and 2 weeks before operation had normal menses. Blood, urine, spinal fluid, throat and vaginal cultures were taken.

The patient was treated with methicillin, ventilation, cardiovascular support and intermittent haemodialysis. She made a slow recovery, losing most of her hair and desquamating her hands and feet with loss of all the toes of her left foot.

From the prostheses and the cavities, non-typable β-lactamase-producing methicillin-sensitive *S. aureus* negative for toxic shock syndrome toxin-1 (TSST-1) production[8] were grown. *Clostridium perfringens* was isolated from the right cavity. Blood, urine and spinal fluid cultures were negative. Specimens from the oral cavity and vagina grew only non-pathogenic commensal micro-organisms.

Discussion

The diagnostic criteria of TSS have been set by the Center for Disease control, USA (*Table 1*)[9]. All criteria were present in this patient. The incubation period can be as short as 12 h but averages 48 h. The disease has been associated with TSST-1-producing *S. aureus*. These strains have been isolated in patients, originating from menstruation and rarely from the blood. Staphylococci from non-menstrual cases of TSS may not produce TSST-1, as in the present case, and other toxins may be involved in the pathogenesis of the syndrome[10].

The majority of TSS is community acquired and associated with menstruation and the use of tampons. It may appear in association with nosocomial infections[4] such as surgical wounds, cutaneous and subcutaneous abscesses, empyema, cellulitis, burns, insect bites, herpes zoster, adenitis, bursitis, fasciitis, septic abortions, mastitis and osteomyelitis.

Certain highly absorbent, semisynthetic tampons promote the growth of *S. aureus* and the production of TSST-1, increasing the risk of TSS. Breast prostheses may present the same risk and seven previously reported cases of TSS after insertion of breast prostheses are recorded (*Table 2*). Meticulous perioperative hygiene and prophylactic perioperative antibiotics should be used[11].

Early recognition is life-saving[12]. Lethality of TSS is 3–10 per cent. When TSS is complicated by disseminated intravascular coagulopathy, adult respiratory distress syndrome and acute tubulointerstitial nephropathy, as in the present case, the mortality rate is very high. It is important to remove all foreign material and debris as soon as possible. An antistaphylococcal antibiotic should be given. Further treatment is according to symptoms.

Table 1 *Definition of toxic shock syndrome*

Main criteria (3 or more)

1. Fever ≥ 39°C
2. Hypotension, systolic blood pressure ≤ 90 mmHg, or orthostatic dizziness
3. Rash, erythema like sunburn, or macular erythroderma
4. Desquamation, particularly of palms and soles

Other criteria (3 or more)

1. Vomiting or diarrhoea
2. Myalgia or creatine phosphokinase $\geq 2 \times$ the upper limit of normal
3. Vaginal, oropharyngeal or conjunctival hyperaemia
4. Serum creatinine or serum urea $\geq 2 \times$ the upper limit of normal, or leucocyturia in the absence of a urinary tract infection
5. Total bilirubin, serum aspartate aminotransferase, or serum lactate dehydrogenase $\geq 2 \times$ the upper limit of normal
6. Platelets $\leq 100 \times 10^9$/l
7. Alterations in consciousness

Exclusion of other infectious causes

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Table 2 *Toxic shock syndrome after insertion of breast prostheses*

	Reference							
	2 (1979)	3 (1981)	4 (1982)	5 (1983)	6 (1986)	7 (1987)	7 (1987)	Present study
Age of patient (years)	32	21	31	32	33	39	57	27
Prosthesis type*	1*	?	?	4*	5*	?	?	8*
Time from operation to								
Toxic shock syndrome (days)	1	?	1	4	1½	3	3	1
Admittance (days)	3	4	?	7	4	†	4	4½
Prostheses removed	+	+	+	+	+	–	+	+
Culture of *Staphylococcus aureus* from								
Operational cavities	+	+	+	+	+	+	+	+
Blood	–	–	–	–	–	–	–	–
Other places	–	–	–	–	–	+	–	–
Other bacteria†	1†	–	–	–	–	–	–	8†
Toxin production	?	?	?	?	+	+	+	–
Disseminated intravascular coagulopathy	+	+	+	+	+	–	–	+
Adult respiratory distress syndrome	+	–	+	+	+	–	–	+
Acute tubulointerstitial nephropathy	+	+	+	+	+	–	–	+
Other complications‡	1‡	2‡	3‡	4‡	–	–	–	8‡
Association with								
Menstruation	?	–	–	+	–	?	?	–
Use of tampons	?	–	–	+	–	?	?	–
Survival	+	+	–	+	+	+	+	+

* Prosthesis type: ?, data not given; † the patient developed toxic shock syndrome during her stay in hospital. 1, silicone gel; 4, bilumen Heyer–Schulte Model no. 360-5325 with 20 mg methylprednisolone in the outer lumen; 5, bilumen 3M style 76 with 0·9 M saline solution in the outer lumen; 8, silicone gel. † Other bacteria: 1, *Klebsiella;* 8, *Clostridium perfringens.* ‡ Other complications: 1, joint swelling, dysaesthesia in the distal extremities; 2, toxic shock syndrome relapse; 3, pneumonia; 4, a large confluent bullous lesion; 8, pericarditis, affection of plexus brachialis, gangrene of the toes

References

1. Todd J, Fishaut M. Toxic-shock syndrome associated with phage-group-I staphylococci. *Lancet* 1978; **ii**: 1116–18.
2. Uretsky BF, O'Brien JJ, Courtiss EH, Becker MD. Augmentation mammaplasty associated with a severe systemic illness. *Ann Plast Surg* 1979; **3**: 445–7.
3. Knudsen F, Olesen AS, Hojbjerg T, Jorgensen JP, Nielsen KK. Toxic shock syndrome. *N Engl J Med* 1981; **282i**: 399.
4. Bartlett P, Reingold AL, Graham DR *et al.* Toxic shock syndrome associated with surgical wound infections. *JAMA* 1982; **247**: 1448–50.
5. Barnett A, Lavey E, Pearl RM, Vistnes LM. Toxic shock syndrome from an infected breast prosthesis. *Ann Plast Surg* 1983; **10**: 408–10.
6. Giesecke J, Arnander C. Toxic shock syndrome after augmentation mammaplasty. *Ann Plast Surg* 1986; **17**: 532–3.
7. Tobin G, Shaw RC, Goodpasture HC. Toxic shock syndrome following breast and nasal surgery. *Plast Reconstr Surg* 1987; **80**: 111–14.
8. Espersen F, Baek L, Kjaeldgaard P, Rosdahl VT. Detection of staphylococcal toxin shock syndrome toxin 1 by a latex agglutination kit. *Scand J Infect Dis* 1988; **20**: 449–50.
9. Center for Disease Control. Toxic-shock syndrome, United States, 1970–82. *Morbid Mortal Wkly Rep* 1982; **31**: 201–4.
10. Garbe PL, Arko RJ, Reingold AL *et al. Stafylococcus aureus* isolates from patients with nonmenstrual toxic shock syndrome: evidence for additional toxins. *JAMA* 1985; **253**: 2538–42.
11. Freedman AM, Jackson IT. Infections in breast implants. *Infect Dis Clin North Am* 1989; **3**: 275–87.
12. Williams GR. The toxic shock syndrome: many cases are not associated with menstruation. *Br Med J* 1990; **300**: 960.

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Chylothorax after oesophagectomy

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Chylothorax is an uncommon complication of oesophagectomy. In a review of 537 oesophageal resections there were 11 cases of chylothorax, an incidence of 2·0 per cent. There was no correlation with site, size, penetration, lymph node status, length or type of tumour but there was a significant correlation between chylothorax and the type of operative procedure carried out. The incidence in 95 transhiatal resections was 10·5 per cent. The incidence following 442 transthoracic procedures was 0·2 per cent (P$<$0·001) *with one chylous fistula occurring after a three-stage oesophagectomy. Initial management was conservative with chest drainage and total parenteral nutrition. Thoracotomy and duct ligation was subsequently carried out in three patients and was successful in two. The third patient died. Conservative management alone was successful in four out of eight patients, with closure of the fistula at a median of 35 days (range 14–42 days). Four patients treated conservatively died. Transhiatal oesohagectomy greatly increases the risk of chylothorax, a condition that carries a high mortality rate (46 per cent in this series) whether managed conservatively or by surgical intervention.*

Chylothorax may result from congenital atresia of the thoracic duct, carcinomatous infiltration, malposition of a subclavian line or blunt chest trauma, but thoracic surgical procedures account for the majority of cases in adults[1]. While it has hitherto been considered an uncommon complication of oesophageal resection[1,2] a recent report has suggested that chylothorax is increasing in incidence[2]. The aims of this study were to examine the factors that might predispose to the development of chylothorax and to review management of the condition.

Patients and methods

The case notes of 537 patients undergoing oesophagectomy on three surgical firms from 1977 to 1990 were reviewed and the incidence of chylothorax was recorded. A variety of surgical procedures was performed, influenced by the site of the tumour and the condition of the patient. Transhiatal resection was reserved chiefly for patients with compromised cardiorespiratory reserve.

Chylothorax was suspected when drainage of straw-coloured fluid from the chest drain continued for more than 5 days and was confirmed as a chylous leak by its milky white appearance following the administration of cream through the nasogastric tube.

Seven parameters were evaluated for their association with the development of chylous fistula: site, size, penetration, lymph node status, length and type of tumour, and the type of operative procedure. Student's t test was used to compare ages between groups. All other factors were compared by the χ^2 test.

Results

Incidence

Of the 537 patients who underwent resection of the oesophagus for carcinoma, 11 (2·0 per cent) developed postoperative chylothorax. All 11 patients presented with excessive drainage of straw-coloured fluid through chest drains placed at the time of operation. The diagnosis of chylothorax was suspected between the second and fifth day after operation (median 3·5 days) and was confirmed by feeding cream through the nasogastric tube which converted the drainage to a milky white colour.

Predisposing factors

There was no correlation between tumour site or size, tumour penetration, lymph node status, tumour length or type and the development of chylous fistula. The type of operation, however, played a significant role. The incidence of fistula in 95 patients who had a transhiatal oesophagectomy was 10·5 per cent. Only one (0·2 per cent) of 442 patients who had a transthoracic operation developed a fistula ($P<0{\cdot}001$) and this occurred following a three-stage operation, of which 99 were performed. There were no fistulae among 197 Lewis–Tanner procedures, 85 midline and left chest approaches, 52 pharyngolaryngo-oesophagectomies and nine other procedures.

Management

All patients were initially managed conservatively with total parenteral nutrition and chest drainage. Conservative management was abandoned in three patients on days 9 or 10 because of persistence of a high volume output and haemodynamic instability. Thoracotomy with duct ligation was performed. Two of these patients survived but one died from sepsis on the 30th day after operation. Eight cases were managed conservatively. The median duration of successful conservative treatment was 35 (range 14–42) days. One patient had a recurrence of the fistula 1 week after discharge. This was treated successfully by the aspiration of 480 ml of fluid, followed by a repeat aspiration of 80 ml 1 week later.

Four patients recovered with conservative management. Four patients died as a result of sepsis between the sixth and 32nd day.

The overall 90-day mortality rate in the series was 46 per cent with no significant difference between conservative and surgical management.

Discussion

The incidence of chylothorax in this series was 2·0 per cent, which is in broad agreement with other series. There was, however, a marked disparity between the incidence following the transhiatal approach and that following the transthoracic approach. The incidence of 0·2 per cent after transthoracic oesophagectomy with a variety of left and right-sided procedures compares favourably with other reports in the literature. Employing the Ivor Lewis procedure, King *et al.* described an incidence of chylothorax of 1 per cent in 100 cases[3], while Woods *et al.* reported an incidence of 2 per cent in 50 cases[4]. Tam *et al.*, using a three-stage procedure, reported an incidence of 0·6 per cent in 316 patients[5]. Skinner *et al.*, using a radical *en bloc* resection, described an incidence of 2·5 per cent in 80 cases[6]. The transhiatal approach has been associated with a wider range of incidence. While Wong's group had no case of chylothorax in a series of 210 patients comprising

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38 transhiatal and 172 transthoracic resections[7], Hankins *et al.* reported an incidence of 3·8 per cent in 26 patients[8], and Orringer *et al.*[9] described an incidence of 3 per cent in 310 patients operated on for a variety of conditions with an incidence of 8 per cent following 24 transhiatal resections for achalasia[10].

The reason for this difference in incidence of thoracic duct damage between techniques is unclear. The thoracic duct has a close anatomical relationship with the oesophagus throughout its course and particularly at the level of the fifth thoracic vertebra where the duct passes from right to left posterior to the oesophagus. It may be argued that while the duct is no more prone to damage with the transhiatal than with the transthoracic approach, any damage which occurs may be more easily identified and corrected peroperatively with transthoracic resection. In this series, however, there was only one case of duct injury recognized and ligated at the time of the original operation. The diagnosis of chylothorax may easily be missed in the early postoperative period, because the fluid is straw-coloured and not the milky white effusion commonly described. This has been commented on by others[9,11] and reflects the fact that these patients are malnourished and fasting. Of the confirmatory tests available, which include lymphography[12] and lymphoscintigraphy[13,14], we have found the ingestion of cream to be reliable, effective and inexpensive. At operation the site of the leak may be identified by administering cream[9], other fats, or methylene blue[15] through the nasogastric tube. In the present group of patients this was unnecessary because mass ligation of the thoracic duct immediately above the diaphragm was carried out.

The management of chylothorax is difficult and individual experience is limited; the largest series in the Western literature contains only 11 patients[9]. Following oesophagectomy a chylous leak is a severe physiological insult, particularly in patients who are already malnourished; the thoracic duct transports up to 4 litres of chyle daily, and this contains up to half of the total body protein. Loss of cellular immune competence further compromises the patient, leaving them ill-equipped to combat infection[16]. Persistence with conservative management, therefore, poses a great challenge in maintaining nutritional support. Thoracotomy with duct ligation, on the other hand, is an unattractive option in a group of patients who have often been selected for transhiatal approach because of inadequate cardiorespiratory reserve.

Jalili[17] successfully treated 34 out of 34 cases of congenital chylothorax conservatively, Puntis *et al.* had success in ten out of 15 children with chylous fistulae from a variety of causes[18], and Schmidt[19] advocated conservative management regardless of the cause. In contrast, Orringer *et al.* advocated operative intervention in all cases of chylothorax and reported no mortality and only one recurrence[9]. They stressed that conservative management is hazardous in an already nutritionally depleted population. However, when the transhiatal approach is reserved largely for patients considered unfit for thoracotomy, a policy of early operative intervention is not easy to pursue. Most authors recommend a staged approach depending on response. Indications for abandoning drainage include drainage of 1 litre per day[20] or 1·5 litres for five consecutive days[2], or persistence of drainage for more than 2 weeks[2,20]. In our series only one of four successful conservatively managed fistulae closed within 14 days, the mean duration of drainage being 31 days. Taba *et al.*[2] have suggested the advent of metabolic complications as an indication for operative intervention but this seems the least appropriate time to abandon conservative management.

Other approaches include pleurodesis at pleuroscopy with talc[21], with tetracyclines[22], or with fibrin glue[23]. Skinner's group[24] evaluated pleuroperitoneal shunting in 29 cases of persistent pleural effusion. Two shunts were for postoperative chylothorax and both patients responded; 83 per cent of the shunts functioned until death. Murphy *et al.* also described success in 12 out of 16 patients treated with a pleuroperitoneal shunt[25].

We conclude that the risk of developing chylothorax after oesophagectomy is significantly greater after the transhiatal approach (10·5 per cent) than after the transthoracic approach (0·2 per cent). The mortality rate is high and in this respect there is no significant difference between conservative management (50 per cent) or ligation of the thoracic duct at surgery (33 per cent). Pleurodesis or pleuroperitoneal shunting may have a role where thoracotomy is definitely contraindicated.

References

1. Servelle M, Nogues CI, Soulie J *et al.* Spontaneous, postoperative and traumatic chylothorax. *J Cardiovasc Surg* 1980; **21**: 475–8.
2. Taba L, Dedhia HV, Bower R, Alexander JC. Chylothorax review. *Crit Care Med* 1985; **13**: 49–52.
3. King RM, Pairolero PC, Trastek VF, Payne WS, Bernatz PE. Ivor Lewis oesophagectomy for carcinoma of the oesophagus: early and late functional results. *Ann Thorac Surg* 1987; **44**: 119–22.
4. Woods SD, McGuire LJ, Chung SC, Crofts TJ, Li AK. Intrathoracic stapled anastomosis after oesophagectomy for carcinoma. *Aust NZ J Surg* 1989; **59**: 647–51.
5. Tam PC, Fok M, Wong J. Re-exploration for complications after oesophagectomy for cancer. *J Thorac Cardiovasc Surg* 1989; **98**: 1122–7.
6. Skinner DB. *En bloc* resection for neoplasms of the oesophagus and cardia. *J Thorac Cardiovasc Surg* 1983; **85**: 59–71.
7. Fok M, Siu KF, Wong J. A comparison of transhiatal and transthoracic resection for carcinoma of the thoracic oesophagus. *Am J Surg* 1989; **158**: 414–19.
8. Hankins JR, Miller JE, Attar S, McLoughlin JS. Transhiatal oesophagectomy for carcinoma of the oesophagus. *Ann Thorac Surg* 1987; **44**: 123–7.
9. Orringer MB, Bluett M, Deeb GM. Aggressive treatment of chylothorax complicating transhiatal oesophagectomy without thoracotomy. *Surgery* 1988; **104**: 720–6.
10. Orringer MB, Sterling MC. Oesophageal resection for achalasia: indications and results. *Ann Thorac Surg* 1989; **47**: 340–5.
11. Romero CS, Navarro TP, Trigo MC, Valdes BAJ, Martin SC. Usefulness of the determination of lipid parameters in pleural effusions. *Med Clin* 1989; **92**: 450–3.
12. Ngan H, Fok M, Wong J. The role of lymphography in chylothorax following thoracic surgery. *Br J Radiol* 1988; **61**: 1032–6.
13. Baulieu F, Baulieu JL, Mesny J *et al.* Visualisation of the thoracic duct by lymphoscintigraphy. *Eur J Nucl Med* 1987; **13**: 264–5.
14. Hvid-Jacobsen K, Nielsen SL, Jensen VJ, Thomsen HS. Demonstration of the thoracic duct by 123 I heptadecanoic acid. *Acta Radiol* 1987; **28**: 783–4.
15. Engevik L. Traumatic chylothorax. *Scand J Thorac Cardiovasc Surg* 1976; **10**: 77–8.
16. Breaux JR, Marks C. Chylothorax causing reversible T-cell depletion. *J Trauma* 1988; **28**: 705–7.
17. Jalili F. Medium chain triglycerides and total parenteral nutrition in the management of infants with congenital chylothorax. *South Med J* 1987; **80**: 1290–3.
18. Puntis JW, Roberts KD, Handy D. How should chylothorax be managed? *Arch Dis Child* 1987; **62**: 593–6.
19. Schmidt A. Chylothorax: review of the 5 year cases in the literature and report of a case. *Acta Chir Scand* 1959; **118**: 5–14.
20. Selle JG, Snyder WH, Schreiber JT. Chylothorax: indications for surgery. *Ann Surg* 1973; **177**: 245–9.
21. Frey JG, Tschopp JM. Chylothorax: treatment using talc pleurodesis. *Schweiz Med Wochenschr* 1987; **117**: 1624–7.
22. Kassel RN, Havas TE, Gullane PJ. The use of topical tetracycline in the management of persistent chylous fistulae. *J Otolaryngol* 1987; **16**: 174–8.
23. Stenzl W, Rigler B, Tscheliessnigg KT *et al.* Treatment of post surgical chylothorax with fibrin glue. *Thorac Cardiovasc Surg* 1983; **31**: 35–7.
24. Little AG, Kadowaki MH, Ferguson MK, Staszek VM, Skinner DB. Pleuroperitoneal shunting. Alternative therapy for pleural effusions. *Ann Surg* 1988; **208**: 443–50.
25. Murphy MC, Newman BM, Rogers BM. Pleuroperitoneal shunts in the management of persistent chylothorax. *Ann Thorac Surg* 1989; **48**: 195–200.

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Preoperative localization of parathyroid tumours does not reduce operating time

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Accurate preoperative localization of abnormal parathyroid glands might be expected to result in a reduction in operating time. To test this hypothesis the duration of surgery was recorded in a consecutive series of 50 patients who underwent neck exploration after preoperative localization by thallium-201 and technetium-99m subtraction scanning and were found to have parathyroid tumours. A total of 34 patients had accurate localization by the scan, and these patients had a median operating time of 90 min. When the tumour had not been localized before operation, the median operating time was not significantly different (80 min). Accurate preoperative localization of parathyroid tumours does not reduce operating time.

The widespread use of biochemical multichannel analysis screening has resulted in primary hyperparathyroidism being diagnosed with increasing frequency. More patients are being referred for neck exploration.

In the hands of an experienced endocrine surgeon an adenoma will be located in 95 per cent of cases[1–4], but for the less experienced this figure may be considerably lower[5]. In many instances surgery may be preceded by an imaging procedure intended to localize the tumours. Currently the two most commonly used techniques are thallium–technetium subtraction scanning and high resolution ultrasonography[6–8].

Where surgeons aim to identify the parathyroid adenoma and at least one normal gland at operation, preoperative localization might shorten operating time[9,10]. It has been suggested that by correctly identifying the side or site of the tumour, one could then explore the other side while awaiting the results of frozen section examination on the material removed[8,11,12].

This study analysed operating time to assess whether accurate preoperative localization was reflected in reduced operating time.

Patients and methods

The study group comprised a consecutive series of 50 patients undergoing first neck exploration by one surgeon (A.E.Y.) for biochemically proven hyperparathyroidism, who were found to have parathyroid tumours and who had undergone preoperative thallium-201–technetium-99m scanning[13].

Operation was a standard neck exploration with a view to identifying and excising the tumours and biopsying at least one normal gland in each patient. At operation the gland identified by the scan as abnormal was sought first and then a normal gland was sought on the same side. While awaiting the results of frozen section the opposite side of the neck was explored, but biopsies only taken if a normal gland had not been found on the same side as the tumour.

Operating time was recorded as the time spent in the operating theatre, after induction of anaesthesia, and included time spent awaiting the results of frozen section histology (usually about 20 min).

Statistical differences have been determined using the Mann–Whitney *U* test.

Results

For the 50 patients studied the median (range) operating time was 85 (40–135) min.

Surgical exploration revealed 52 parathyroid tumours in 50 patients. A total of 47 patients had single adenomas, and two patients had two adenomas on one side of the neck. One patient was found to have a parathyroid carcinoma. Tumours in 34 patients were accurately localized before operating by subtraction scanning, including the patient with the carcinoma, and one of the patients with double adenomas (70 per cent).

The median (range) operating time of 90 (40–130) min for parathyroid tumours accurately localized did not differ significantly from that where the tumour was not localized before operation, 80 (50–135) min.

Throughout the 8 years of this study, a statistically significant trend towards a shorter operating time in the later years was observed (*Figure 1*). This same trend was observed within the tumour group whether accurately localized or not.

Discussion

It has been shown that an experienced surgeon will locate upwards of 95 per cent of parathyroid lesions at initial exploration. Because the accuracy of localization is at best 80 per cent, it has been suggested that in the previously unexplored neck preoperative localization is not necessary[11,14,15]. Indeed, it has been said the best localization is to locate an experienced parathyroid surgeon[16].

Proponents of preoperative localization claim that it reduces operating time and reduces the incidence of missed adenomas and persistent hyperparathyroidism, especially for ectopically situated adenomas. By limiting dissection it should reduce operative complications such as recurrent laryngeal nerve damage, and permanent hypocalcaemia[6,9,17]. Over the past decade an increasing number of neck explorations are being performed on asymptomatic patients, in cases where the adenoma is likely to be small, and often by inexperienced surgeons outside recognized specialist centres. In such circumstances it has been shown that a higher incidence of persistent hyperparathyroidism results[18], and in these cases accurate preoperative localization might be expected to be valuable.

For the experienced parathyroid surgeon preoperative localization before first exploration is not likely to shorten operative time. Are there any instances where it is useful? Clearly it is of value before reoperation. Some patients fear the exploratory nature of a parathyroid operation and here a subtraction scan depicting an adenoma may be a significant reassurance[19]. For those using unilateral neck exploration as the initial operation for primary hyperparathyroidism, preoperative localization is clearly of central importance[20]. In patients with a fixed flexion deformity of the neck (as occurred in two patients in this series), bilateral exploration may be difficult, and in this unusual setting accurate localization is advantageous.

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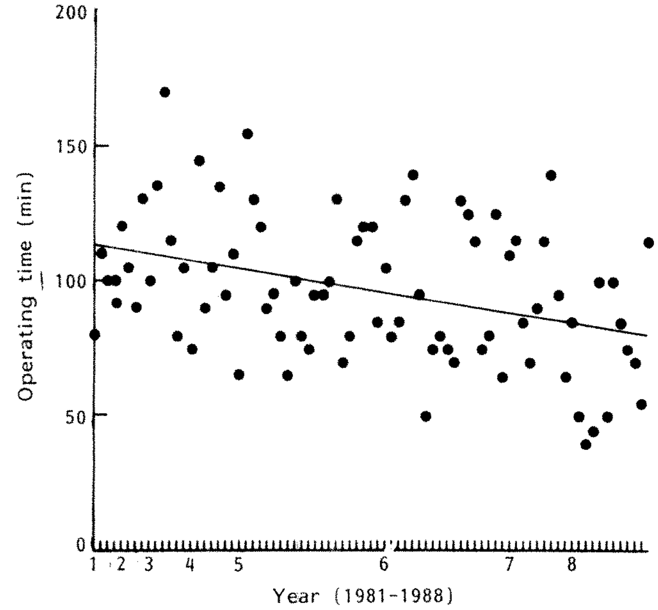

Figure 1 *Operating time for the total series of parathyroidectomies between 1981 and 1988 was significantly shorter for patients operated upon between 1986 and 1988, compared with the period 1981 to 1985* (P = *0·007*)

Wheeler and Wade using preoperative localization with methylene blue, reported a reduction in operating time[21]. Hauty *et al.*[11] showed a statistically non-significant 15 per cent reduction in operating time in those not scanned compared with correctly scanned patients. Attie *et al.*[12] showed a reduction in operating time by 30–50 per cent for correctly localized adenomas. Neither series fully detailed operating times for the total series nor gave any statistical analysis.

This study failed to detect any significant difference in operating time when comparing accurately localized parathyroid tumours to those not localized.

The requirements for successful parathyroid surgery remain experience, patience, a bloodless field and a systematic dissection founded on the principles of parathyroid anatomy and embryology[22]. In the previously unexplored neck, preoperative localization of parathyroid lesions does not allow any of these principles to be bypassed and surgery is neither quicker nor more effective.

References

1. Satava RM, Beahrs OH, Scholz DA. Success rate of cervical exploration for hyperparathyroidism. *Arch Surg* 1975; **110**: 625–7.
2. Bruining HA, VanHouten H, Juttman JR, Lamberts SWJ, Birkenhagen JC. Results of operative treatment of 615 patients with primary hyperparathyroidism. *World J Surg* 1981; **5**: 85–90.
3. Hines JR, Atiyah R, Kliefoth J, Beal JM. Hyperparathyroidism: problems in surgical treatment. *Am J Surg* 1982; **144**: 504–10.
4. Bainbridge ET, Barnes AD. Some changing aspects of primary hyperparathyroidism. *Ann R Coll Surg Engl* 1983; **65**: 67–70.
5. Palmer JA, Rosen IB. Reoperative surgery for hyperparathyroidism. *Am J Surg* 1982; **144**: 406–10.
6. MacFarlane SD, Hanelin LG, Taft DA, Ryan JA, Fredlund PN. Localisation of abnormal parathyroid glands using thallium-201. *Am J Surg* 1984; **148**: 7–11.
7. Levin KE, Clark OH. Localisation of parathyroid glands. *Ann Rev Med* 1988; **39**: 29–40.
8. Roses DF, Sudarsky LA, Sanger J, Raghavendra BN, Reede DL, Blum M. The use of preoperative localisation of adenomas of the parathyroid glands by thallium–technetium subtraction scintigraphy, high-resolution ultrasonography and computed tomography. *Surg Gynecol Obstet* 1989; **168**: 99–106.
9. Gupta SM, Belsky JL, Spencer RP *et al.* Parathyroid adenomas and hyperplasia. Dual radionuclide scintigraphy and bone densitometry. *Clin Nucl Med* 1985; **10**: 243–7.
10. Manni A, Basarab RB, Plourde PV, Koivunen D, Harrison TS, Santen RJ. Thallium–technetium parathyroid scan. A useful non-invasive technique for localisation of abnormal parathyroid tissue. *Arch Intern Med* 1986; **146**: 1077–80.
11. Hauty M, Swartz K, McChung M, Lowe DK. Technetium–thallium scintiscanning for localisationof parathyroid adenomas and hyperplasia. *Am J Surg* 1987; **153**: 479–86.
12. Attie JN, Khan A, Rumancik WM, Moskowitz GW, Hirsch MA, Herman PG. Preoperative localisation of parathyroid adenomas. *Am J Surg* 1988; **156**: 323–6.
13. Young AE, Gaunt JI, Croft DN, Collins REC, Wells CP, Coakley AJ. Localisation of parathyroid adenomas by thallium-201 and technetium-99m subtraction scanning. *Br Med J* 1983; **286**: 1384–6.
14. Okerlund MD, Sheldon K, Corpuz S *et al.* A new method with high sensitivity and specificity for localisation of abnormal parathyroid glands. *Ann Surg* 1984; **200**: 381–8.
15. Rosoff L. Presidential address: hyperparathyroidism, hypergraphia and just plain hype. *Surgery* 1985; **98**: 989–94.
16. Thompson NW. Localisation studies in patients with primary hyperparathyroidism. *Br J Surg* 1988; **75**: 97–98.
17. Davidson J, Noyek AM, Gottesman I *et al.* The parathyroid adenoma: an imaging/surgical perspective. *J Otolaryngol* 1988; **17**: 282–7.
18. Malmaeus J, Granberg PO, Halvorsen J, Akerstrom G, Johansson H. Parathyroid surgery in Scandinavia. *Acta Chir Scand* 1988; **154**: 409–13.
19. Duh QY, Sancho JJ, Clark OH. Parathyroid localisation. *Acta Chir Scand* 1987; **153**: 241–54.
20. Tibblin S, Bondeson AG, Ljungberg O. Unilateral parathyroidectomy in hyperparathyroidism due to single adenoma. *Ann Surg* 1982; **195**: 245–52.
21. Wheeler MH, Wade SJH. Intraoperative identification of parathyroid glands: appraisal of methylene blue staining. *Am J Surg* 1982; **143**: 713–16.
22. Cohn KH, Silen W. Lessons of parathyroid reoperations. *Am J Surg* 1982; **144**: 511–17.

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Breast cancer in elderly women: a Cancer Research Campaign trial comparing treatment with tamoxifen and optimal surgery with tamoxifen alone

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Three hundred and eighty-one women with operable breast cancer aged over 70 years were randomly allocated to 40 mg tamoxifen daily and optimal surgery or to tamoxifen alone. At a median follow-up of 34 months there was no demonstrable difference in survival rate or in quality of life between the two treatment groups. More patients treated with tamoxifen alone had a subsequent change of management and this was usually an operation for local treatment failure. This progression to surgery has not been shown to be disadvantageous and the study will continue. Informed consent for randomization was difficult to obtain, leading to the exclusion of eligible patients, and it is therefore proposed to include non-randomized patients in a total cohort study.

The incidence of breast cancer increases with age[1] and a third of new tumours occur in women aged over 70 years[2,3]. Women in this age group have usually been excluded from clinical trials despite expectancy of life at age 70 being 14 years and the increase in the number of elderly women[4].

Current clinical management of elderly women with breast cancer varies. Women with the same stage of disease may be treated in different centres by mastectomy[5,6], by local excision[7] or, more recently, by tamoxifen alone[8–13]. Trials of adjuvant tamoxifen in women undergoing surgery for primary breast cancer have shown a definite survival benefit in postmenopausal women[14]. There is therefore an ethical difficulty in withholding tamoxifen from elderly patients. Evidence from uncontrolled studies shows that tamoxifen is effective as the sole primary treatment of operable breast cancer, and an increasing number of elderly women are treated in this way. It was decided therefore that all patients should have tamoxifen but that one group should undergo the surgical procedure that the surgeon felt best suited to the individual patient.

The premise was that tamoxifen is of value as the sole primary treatment of operable breast cancer in the elderly. The question was whether surgery improves the control of disease, the quality of life or the length of survival.

Patients and methods

The study was a randomized multicentre trial co-ordinated by the Cancer Research Campaign Clinical Trials Centre at King's College Hospital.

All women aged over 70 years with operable breast cancer (diagnosed on Tru-Cut® (Travenol Laboratories Incorporated, Deerfield, Illinois, USA) biopsy, fine needle aspiration cytology or unequivocal mammography) with normal radiography of the chest, pelvis and lateral lumbar spine were eligible. Exclusions included patients who declined surgery at the outset, those considered unfit for surgery, and those wth Paget's disease, bilateral breast cancer or an impalpable tumour discovered by mammography. Patients were randomly allocated to either surgical or conservative treatment groups.

The surgeon undertook the operation that was considered best for the individual patient (optimal surgery), for example simple excision or mastectomy. The patient received adjuvant tamoxifen, 40 mg daily (either single or divided dose), indefinitely thereafter.

In the conservative group all patients received the same dose of tamoxifen indefinitely and the tumour response was assessed by Union International Contra le Cancrum criteria[15]. Treatment options, including surgery, could change at 6 months or earlier if tumour growth was progressive ($\geqslant$25 per cent increase over initial maximum diameter).

Tumour progression in the conservatively treated group could not be compared with local recurrence in the surgically treated group and the interval to the first change of management was recorded as an indication of primary treatment failure. The length of survival was used as an outcome measure but death from intercurrent disease is common in this age group and difficult to identify[16–18].

Quality of life was assessed in those centres agreeing to the study using a sociodemographic questionnaire and the General Health Questionnaire (GHQ 28 items)[19]. The GHQ-28 was designed for use as a screening instrument to detect psychiatric and social morbidity and a threshold score of five determines dysfunction. Some[20] have suggested that a threshold score of ten is more appropriate in women with breast cancer undergoing cytotoxic chemotherapy. The two self-report questionnaires were sent to patients by post at least 3 months after operation or from the start of medical therapy.

Survival

The majority of patients were 'flagged' at the National Health Service Central Register which provided the trials office with an automatic notification of the death of each patient within about 6 months. In this analysis, therefore, all patients were assumed to be alive at a cut-off date of 31 March 1989 unless a copy of the death certificate had been previously received (for the few patients from Ireland who could not be 'flagged', a cut-off date of 31 December 1988 was selected to provide time for notification of death).

Statistical methods

Comparison of the two groups for both survival rates and time to change of management used standard log rank χ^2 tests.

Results

By 31 July 1989, 381 patients were entered with a median follow-up of 34 months (*Table 1*). Twenty-seven patients were excluded from analysis because they entered after the cut-off date. Ten patients in the surgically treated group did not undergo surgery, eight because they declined and one developed skin secondaries by the time of admission. In one case information is not available. Of these ten patients, seven are still alive, six with no change of management; three have died, two with and one without a change of management.

First change of management: There was an excess of local treatment failure in the conservatively treated group (64 patients) compared with the surgically treated group (33

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Table 1 *Comparison of treatment groups*

	Surgery ($n=171$)	Conservative treatment ($n=183$)
Median age (years)	76·8	76·6
Mean tumour size (cm)	3·5	3·4
Median follow-up (months)	34·8	33

Table 2 *Reasons for first change of management*

	Surgery ($n=171$)*	Conservative treatment ($n=183$)
No operation	10	—
Local recurrence/progression	12 (7·5)	42 (23·0)
Ipsilateral axillary nodes	6 (3·7)	2 (1·1)
Local recurrence/progression with positive axillary nodes	4 (2·5)	7 (3·8)
Distant recurrence	6 (3·7)	6 (3·3)
Other	9 (5·6)	11 (6·0)
Total	33† (20·5)	64† (35·0)

Values in parentheses are percentages. * Percentages in the surgery group are calculated on the 161 patients who had an operation. † Because recurrence occurs concurrently at local and distant sites in some patients, the total number of patients is less than the sum of all the reasons for a change of management

Table 3 *Locoregional recurrence following surgery in 161 assessable patients*

	Surgical group	Local recurrence
Local excision	120	20 (16·7)
Mastectomy	37	1 (2·7)
Quadrantectomy	4	0
Total	161	21* (13·0)

Values in parentheses are percentages. * Excluded from this analysis was one patient whose surgical procedure was not known and nine patients who refused surgery, one of whom now has progressive disease

Table 4 *Tumour response in the conservative group* (n = *183*)

	Percentage of patients responding	
	At 6 months	Best ever
Complete remission	16·1	32·7
Partial remission	9·0	14·6
No change	62·6	46·8
Progression	12·3	5·8
No. of patients not assessable	28	12

patients) (*Table 2*), leading to further surgery in 35 patients and 15 patients respectively, a statistically significant difference ($\chi^2 = 11{\cdot}35$, $P = 0{\cdot}001$) (*Figure 1*). Local recurrence following surgery is detailed for the 161 assessable patients in *Table 3*.

Tumour responses to tamoxifen alone at 6 months and the best ever are shown in *Table 4*.

There was little difference in the mortality rates between the two groups, with 26 deaths in the surgically treated group and 32 in the group on tamoxifen alone (*Figure 2*).

Twenty-three of the 32 clinicians involved used the quality of life assessment questionnaires on their patients. Of 308 women sent questionnaires, 298 were still alive and 237 responded (79·5 per cent compliance). The mean time between operation and questionnaire response was 13·5 months (range 3–33 months) for the medically treated group it was 12 months (range 3–32 months). The two groups were well matched for sociodemographic characteristics (*Table 5*).

Half of the women in each group lived alone. Most were happy living in their current house and the majority felt that they had someone to talk to about any problems. There was no demonstrable difference between the two groups in their ability to manage household tasks. Approximately one-third of all patients experienced significant difficulty. Using the GHQ overall threshold of five, 30 of 117 women (25·6 per cent) in the surgically treated group had problems indicative of the psychiatric morbidity compared with 33 of 120 (27·5 per cent) women in the other group (*Figure 3*). Using the threshold of ten, the respective numbers of women were 17 (14·5 per cent) and 21 (17·5 per cent). The GHQ-28 contains four subscales for physical malaise, anxiety, social dysfunction and depression but there was no significant difference in the psychosocial morbidity between the two groups.

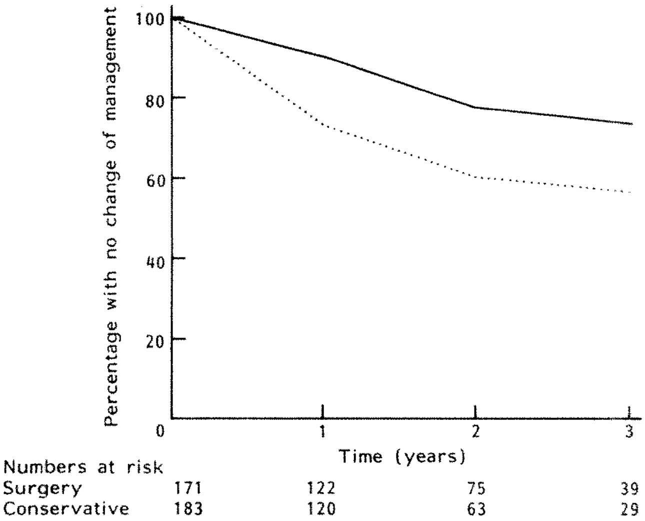

Figure 1 *Log rank comparison of time to first change of management* ($\chi^2 = 11{\cdot}35$, $P < 0{\cdot}001$, *relative risk* $= 0{\cdot}50$, *95 per cent confidence interval* $0{\cdot}33$–$0{\cdot}75$); (——), *surgery;* (-----), *conservative treatment. 'Numbers at risk' represent the number of patients with no change of management at entry and annually thereafter*

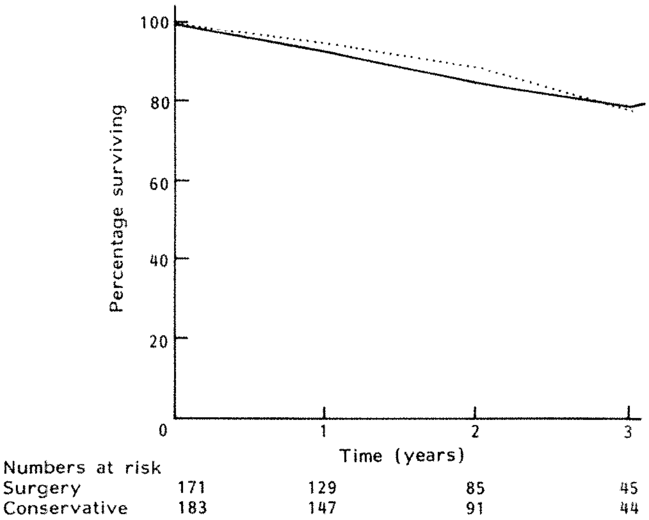

Figure 2 *Overall survival rates* ($\chi^2 = 0{\cdot}25$, $P = 0{\cdot}6$, *relative risk* $= 0{\cdot}88$, *95 per cent confidence interval* $0{\cdot}52$–$1{\cdot}47$); (——), *surgery;* (-----), *conservative treatment. 'Numbers at risk' represent the number of patients alive at entry and annually thereafter*

Table 5 *Social/demographic characteristics*

	Surgery ($n = 117$)	Conservative treatment ($n = 120$)
Marital status		
Married	37 (32)	43 (36)
Widowed	65 (56)	61 (51)
Single	14 (12)	13 (11)
Divorced	1 (1)	3 (3)
Living alone	59 (50)	61 (51)
Unable to manage household tasks	36 (31)	44 (37)
Not happy living in current house	5 (4)	10 (8)
Someone to talk to about problems	102 (87)	106 (88)

Values in parentheses are percentages

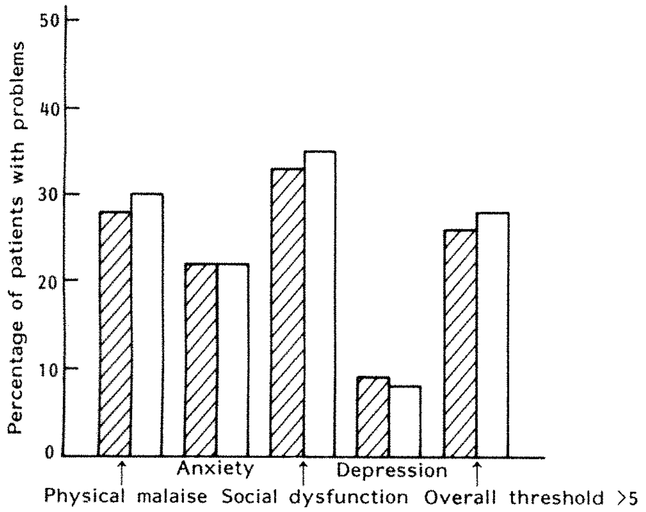

Figure 3 *General Health Questionnaire (GHQ-28);* ▨, *surgery and tamoxifen* (n = *117*); ☐, *tamoxifen alone* (n = *120*)

Discussion

Preliminary reports on two clinical trials of tamoxifen *versus* surgery in the elderly have been published. The St. George's Hospital study[21] had a large proportion of T_3/T_4 tumours, and a 37 per cent locoregional recurrence rate in the surgically treated group led to the conclusion that tamoxifen was the best primary treatment. The Nottingham group studied patients more comparable to those in the present study and found a 43 per cent local treatment failure rate at 3 years with tamoxifen alone: the contrary conclusion was drawn[22]. The discrepancy between the tumour response rates in this and the present study may reflect a difference of interpretation between a tightly controlled single-centre study and a multicentre trial. Two EORTC (European Organisation for Research and Treatment of Cancer) trials of surgery *versus* tamoxifen in the elderly are as yet unpublished. The present study is the only one to examine the effect of surgery with adjuvant tamoxifen in this age group and shows this combination of treatments to be best. Some patients treated with tamoxifen alone require surgery due to local treatment failure but this has not been shown to be disadvantageous so far.

Quality of life is adversely affected by both the diagnosis and treatment of breast cancer but there is no evidence that either treatment in the present study had a more detrimental impact.

If further follow-up in this study demonstrates that the majority of women die from intercurrent disease before symptomatic progession of breast cancer, then tamoxifen alone may be judged to be optimal therapy. If an unacceptable level of local problems persists in those treated conservatively, leading to high surgical intervention rates or locally advanced disease in ageing women less fit to withstand surgery, then a more aggressive initial approach may be justified. Alternatively, new developments in fine needle aspiration cytology with immunohistochemical assessment of oestrogen and other receptors may allow a more selective policy in the future[23–26].

It is felt ethically justifiable to continue with the present study but it has been found difficult to obtain informed consent from some elderly women. An unknown number of potentially eligible women have thereby been excluded and this must raise doubts about the applicability of the conclusions. In future, all eligible patients, after suitable explanation, will be offered the choice of either of the two treatments or of randomization. In this way all patients at risk will be studied[27].

Since 10 October 1990, 40 patients have been entered into the trial and 54 non-randomized patients have been registered.

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References

1. Berg JW, Robbins GF. Modified mastectomy for older, poor risk patients. *Surg Gynecol Obstet* 1961; **13**: 631–4.
2. Haagensen CD. The frequency and age distribution of mammary carcinoma. In: *Diseases of the Breast*. 2nd ed. Philadelphia: WB Saunders, 1971: 348–53.
3. *Cancer in Connecticut: Incidence and Rates (1935–1962)*. Connecticut State Department of Health, 1966.
4. Office of Populations, Censuses and Surveys, 1985–87.
5. Goldenberg IS, Bailar JC, Eisenberg H. Survival of elderly women with breast cancer. *Arch Surg* 1969; **99**: 649–51.
6. Leis HP, Mersheimer WL, Varadi J, Hirose T. Breast cancer in the ninth and tenth decades. *J Am Geriatr Soc* 1964; **12**: 527–37.
7. Reed MWR, Morrison JM. Wide local excision as the sole primary treatment in elderly patients with carcinoma of the breast. *Br J Surg* 1989; **76**: 898–900.
8. Preece PE, Wood RAB, Mackie CR, Cuschieri A. Tamoxifen as initial sole treatment of localised breast cancer in elderly women: a pilot study. *Br Med J* 1982; **284**: 869–70.
9. Helleberg A, Lundgren B, Norin T, Sander S. Treatment of early localised breast cancer in elderly patients by tamoxifen. *Br J Radiol* 1982; **55**: 511–15.
10. Bradbeer J, Kyngdon J. Primary treatment of breast cancer in elderly women with tamoxifen. *Clin Oncol* 1983; **9**: 31–4.
11. Allan SG, Rodger A, Smyth JF, Leonard RCF, Chetty U, Forrest APM. Tamoxifen as primary treatment of breast cancer in elderly or frail patients: a practical management. *Br Med J* 1985; **290**: 358.
12. Margolese RG, Foster RS. Tamoxifen as an alternative to surgical resection for selected geriatric patients with primary breast cancer. *Arch Surg* 1989; **124**: 543–51.
13. Falk GL, Gwynne-Jones D, Gray JG. Efficacy of tamoxifen as the primary treatment of operable breast cancer in the high risk patient. *Aust NZ J Surg* 1989; **59**: 543–5.
14. Early Breast Cancer Trialists' Collaborative Group. Effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer. An overview of 61 randomised trials among 28 896 women. *N Engl J Med* 1988: **319**: 1681–92.
15. Hayward JL, Carbone PP, Hewson J-C, Kumoska S, Segaloff A, Rubens RD. Assessment of response to therapy in advanced breast cancer. *Br J Cancer* 1977; **35**: 292.

16. Hunt KE, Fry DE, Bland KI. Breast carcinoma in the elderly patient: an assessment of operative risk, morbidity and mortality. *Am J Surg* 1980; **140**: 339–42.
17. Schottenfeld D, Robbins GF. Breast cancer in elderly women. *Geriatrics* 1971; **26**: 121–31.
18. Mueller CB, Ames F, Anderson GD. Breast cancer in 3558 women: age as a significant determinant in the rate of dying and causes of death. *Surgery* 1978; **83**: 123–32.
19. Goldberg DP, Cooper B, Eastwood MR *et al.* A standardised psychiatric interview for use in community surveys. *Br J Soc Prev Med* 1970; **24**: 18–26.
20. Hughson AVM, Cooper AF, McArdle CS, Smith DC. Validity of the General Health Questionnaire and its subscales in patients receiving chemotherapy for early breast cancer. *J Psychosom Res* 1988; **32**: 393–402.
21. Gazet JC, Markopoulos CH, Ford HT, Coombes RC, Bland JM, Dixon RC. Prospective randomised trial of tamoxifen *versus* surgery in elderly patients with breast cancer. *Lancet* 1988; **i**: 679–81.
22. Robertson JFR, Todd JH, Ellis IO, Elston CW, Blamey RW. Comparison of mastectomy with tamoxifen for treating elderly patients with operable breast cancer. *Br Med J* 1988; **297**: 511–14.
23. Coombes RC, Powles TJ, Berger U *et al.* Prediction of endocrine response in breast cancer by immunocytochemical detection of oestrogen receptor in fine needle aspirates. *Lancet* 1987; **ii**: 701–13.
24. Gaskell DJ, Hawkins RA, Sangsterl K, Chetty U, Forrest APM. Relation between immunocytochemical estimation of oestrogen receptor in elderly patients with primary breast cancer in response to tamoxifen. *Lancet* 1989; **i**: 1044–6.
25. Heyderman E, Ebbs SR, Larkin SE, Brown BME, Haines AMR, Bates T. Response of breast carcinoma to endocrine therapy predicted using immunostained pelleted fine needle aspirates. *Br J Cancer* 1989; **60**: 630–3.
26. Nicholson S, Halcrow P, Sainsbury JRC *et al.* Epidermal growth factor receptor status associated with failure of primary endocrine therapy in elderly post-menopausal patients with breast cancer. *Br J Cancer* 1988; **58**: 810–14.
27. Schumacher M, Davis K. Combining randomised and nonrandomised patients in the statistical analysis of clinical trials. *Recent Results Cancer Res* 1988; **111**: 130–7.

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Announcement

Association of Head and Neck Oncologists of Great Britain
Founded 1968

The raison d'etre of the Association of Head and Neck Oncologists of Great Britain is the excitement and interest engendered by meeting with colleagues in surgery, clinical oncology, pathology and basic science and the resulting broadening of approach and potential for improving chemical practice.

Our regular annual meeting at which members' papers are proffered provides a catalyst for much multidisciplinary discussion. The Nunn endowment enables us to invite a speaker of international distinction and to cement our liaisons with similar multidisciplinary societies, both in North America and in Europe.

The Association of Head and Neck Oncologists of Great Britain thinks it extremely important to encourage junior staff of all related disciplines and they are actively welcomed to the meeting. In addition, there are scholarships supported by the Nunn Foundation which help young Head and Neck Oncologists to benefit from experience gained by visiting other centres of international repute.

If you are involved in the management of head and neck cancer, we want you to join the Association of Head and Neck Oncologists of Great Britain and, with your junior staff, to participate in our meetings.

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In situ venous valve construction

A technique of in situ *deep venous valve construction based on vein wall intussusception is described. The technique has been used to construct a size-matched, autogenous valve in the femoral vein of the dog. Forty-one valves have been constructed. Immediately after construction, all 41 were patent at ascending phlebography and Harvey's test showed them to be competent. Descending phlebography demonstrated competence in 38 valves. Hydrostatic testing was performed on 27 valves in the vertical position at pressure gradients in the range 0·2–250 cmH_2O. Of these, 24 valves were fully competent. Six valves were studied at intervals between 1 and 112 days after construction. All six were competent by Harvey's test and five were competent at descending phlebography. There was no evidence of thrombosis in any valve. This technique may be suitable for replacement of deep venous valves in patients with the calf pump failure syndrome caused by deep venous reflux.*

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Two large surveys[1,2] suggest that the prevalence of venous ulceration in the UK is approximately 0·25 per cent of the population[3]. The prevalence of less severe calf pump failure is difficult to assess, but it is probably four to five times greater than this[4].

After ulcer healing, indirect or palliative measures including the wearing of graduated compression stockings are employed to prevent ulcer recurrence and to control lesser symptoms. Ideally, calf pump failure would be treated by direct correction of the causative haemodynamic abnormalities, which principally include venous reflux and obstruction. Superficial venous reflux is found in a significant number of patients with venous ulceration[5,6], usually in conjunction with communicating vein incompetence. Correction of these abnormalities is highly successful at preventing recurrent ulceration in the absence of post-thrombotic disease[7]. Deep vein reflux is a major cause of calf pump failure and has been identified in up to 90 per cent of patients with venous ulceration[8]. In our experience, post-thrombotic disease is present in 95 per cent of patients with deep vein reflux[3], although primary deep valve incompetence appears common in other centres[9,10]. Various methods have been described for the repair[11–14] and replacement[15,16] of deep vein valves, including a technique of vein wall intussusception described by Eiseman and Malette[17]. Vein valve mechanism replacement is suitable for correction of primary (non-thrombotic) and post-thrombotic deep vein reflux, whereas valve repair techniques are appropriate only in the former condition, which in our experience is rare. Valve repair, therefore, appears to be of limited value.

Valve transposition[15] and autotransplantation[16] have high long-term patency rates in contrast to methods using homograft[18], prosthetic[19,20] and xenograft[21] materials. No technique, however, appears to provide satisfactory long-term valvular competence and abolition of reflux with maintained resolution of ulceration and lipodermatosclerosis. Suitable size-matched and competent valves can be difficult to obtain for autotransplantation and transposition procedures. In addition, few studies have attempted to define the hydrostatic properties of valve replacement techniques[22]. No dynamic studies have been reported.

We have developed a technique of *in situ* deep vein valve construction based on vein wall intussusception and have studied the short-term properties of this mechanism in the dog. We have used the cusp proportions described by Eiseman and Malette[17] but have added an interposition graft to avoid excessive dissection and tension and we used non-penetrating sutures and clips. The second innovation is the anchoring of the intussuscipiens to produce a distinct bicuspid mechanism with commissures (*Figure 1*).

Materials and methods

Forty-one deep vein valves have been constructed in the hind limbs of 34 dogs weighing 23–34 kg. After initial phlebographic studies in all, 27 were removed for immediate hydrostatic bench testing. Six valves were studied at intervals between 1 and 112 days after construction.

Technique of in situ *vein valve construction*

Adult dogs were anaesthetized using sodium phenobarbitone 30 mg/kg administered as a bolus injection via a superficial forelimb vein. No muscle relaxation was used. The airway was controlled by endotracheal intubation.

The femoral vein was exposed through a vertical incision on the medial aspect of the upper leg and its diameter measured using a pair of callipers. The vein was then mobilized, taking care to remove all adventitia and to ligate all side branches with 3/0 silk. The valve site was then chosen and marked with four lines 1·5 diameters apart (*Figure 2a*). Line 1 marked the upper level of the cusps where the commissures were to be secured. Line 2, drawn down to the level of line 4, formed the base of the valve and the floor of the valve sinus. Line 3 intussuscepted upwards to make the cusp edges when secured at two diametrically opposed points at the level of line 1, which became the two cusp commissures. The method of intussusception is described below. Because lines 2 and 4 were the equivalent of three diameters apart and were pulled together, the technique required a length of vein equal to three times its diameter. The vein was therefore lengthened by using an interposition graft, equal in length to three times the diameter (7·5–10·5 mm) of the vein, which was placed proximal or distal to the valve mechanism, avoiding ligated side branches and native valves in the region of the newly constructed valve. In non-surviving animals whose valves were harvested immediately after construction for bench testing, the vein was lengthened by inserting an expanded polytetrafluoroethylene (ePTFE) graft mounted on two solid PTFE stents after giving heparin (200 units/kg) by intravenous bolus injection. No other anticoagulant was administered to any animal. In surviving animals whose valves were studied at varying intervals after construction, the vein was lengthened with an external jugular vein interposition graft. The insertion of the interposition graft was the only part of the procedure requiring clamping of the vein and luminal occlusion. The valve mechanism was constructed with the clamps off and with blood flowing.

Having placed the interposition graft, the valve mechanism was constructed. Two 5/0 Prolene® (polypropylene; Ethicon Ltd., Edinburgh, UK) sutures, diametrically opposed, were passed through the vein at the level of line 1 (*Figure 2a*). Both sutures were then passed down the lumen of the vein to the level of line 3 where they were passed through the wall. They were then passed back into and up the lumen, out through the wall at the level of line 1 and through a 2 mm diameter

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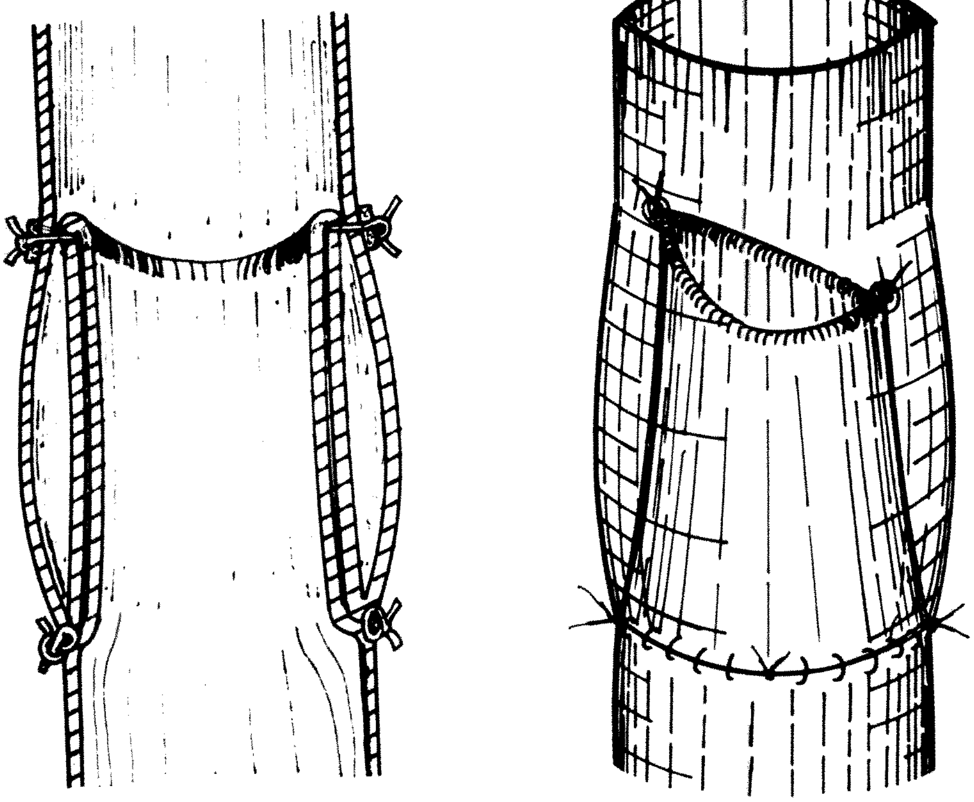

Figure 1 In situ *valve construction by vein wall intussusception to produce a bicuspid mechanism with one common sinus*

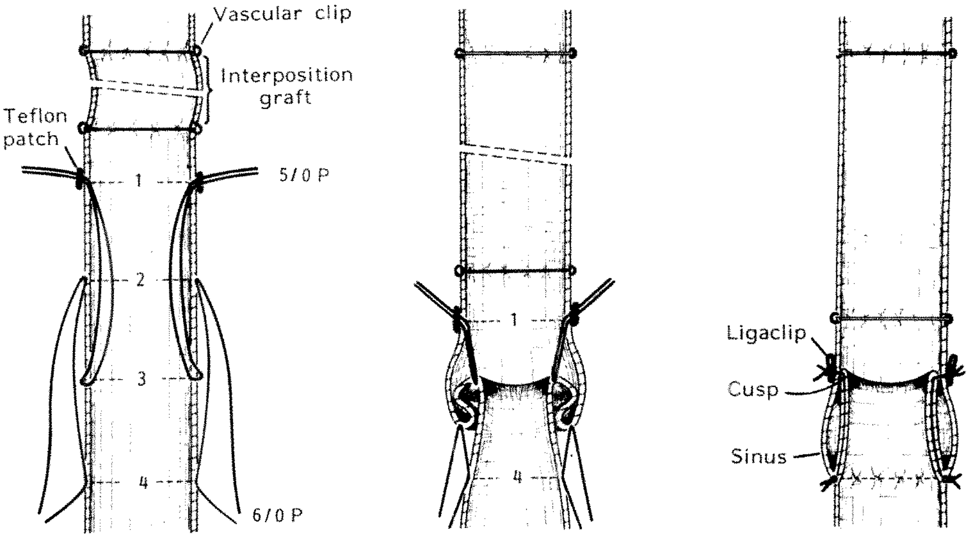

Figure 2 *Technique of* in situ *valve construction (see text for details). P, Prolene*

Teflon® (E.I. du Point de Nemours and Company, UK) patch. Four 6/0 Prolene sutures were then passed, at equal intervals around the circumference of the vein, through the muscularis (but not into the lumen) at the levels of lines 2 and 4 (*Figure 2a*). All these sutures were held loosely with rubber-shod clips. The four 6/0 sutures were then gradually tightened, pulling line 2 towards line 4 while the two 5/0 sutures were tightened, intussuscepting the vein, at line 3 until it reached line 1 (*Figure 2b*). The cusp commissures were formed by tying the 5/0 sutures over the Teflon patches and a Ligaclip® (Ethicon) was applied to the Teflon patch to mark the level of the commissures at phlebography. The four 6/0 sutures were tied, once lines 2 and 4 were fully opposed, to form the base of the valve sinus (*Figure 2c*). The full circumference of the base of the valve was then secured by holding the two layers of vein wall together with non-penetrating silver clips (developed by Professor W. M. Kirsch, Loma Linda Medical College, California, USA), which pinch the vein walls together without entering the lumen. In three surviving animals the external jugular vein interposition graft anastomosis was fashioned using these clips. The vein was kept moist throughout the procedure by irrigating with heparinized saline and every effort was made to handle it gently. No attempt was made to destroy the native valves.

After the valve was constructed, its competence was checked using Harvey's test[23]. This involves emptying the valve and adjacent vein by gentle digital compression. Proximal compression is then released allowing retrograde flow into the valve while preventing antegrade flow of blood back into the valve by continued distal compression. Filling of the valve segment with continued collapse of the distal vein indicates valve competence.

A 14 French gauge cannula was then inserted into the vein above the valve and secured with a 5/0 Prolene purse string suture for descending phlebography. The tip of the cannula was positioned just proximal to the level of the cusp commissures. Care was taken to ensure that no native valve came between the cannula tip and the constructed valve. The wound was then closed in layers to restore normal tissue pressures round the valve.

Assessment of valve function

Phlebography. An ascending phlebogram was performed to confirm patency and to exclude any gross technical error (*Figure 3a*) by injecting 30 ml of Niopam® (E. Merck Ltd., Four Marks, UK) via a 16-gauge Teflon cannula inserted into a distal tributary. A tourniquet was applied just above the cannulation site. A descending phlebogram was performed to confirm competence of the valve (*Figure 3b*) by injecting 5 ml Niopam by hand via the cannula inserted above the valve. During injection a Valsalva manoeuvre was mimicked by a period of sustained positive pressure ventilation. This provoked deep venous reflux as indicated by distension of the valve-bearing segment, although venous pressure and flow were not measured.

Hydrostatic bench testing. Following phlebographic assessment, the femoral vein was ligated 2 cm above and below the valve and the valve was excised for bench testing. The valve-bearing vein segment was mounted on an adjustable jig so that the cusp commissures and valve base were the same distance apart (1·5 diameters) as before removal, to restore the *in vivo* dimensions and vessel wall tensions. The construction of the jig allowed antegrade and retrograde perfusion of the valve. Antegrade flow was confirmed and valve competence was studied by measuring its ability to support a column of water above the open-ended valve (*Figure 4*). The water column was fed by a header tank to maintain a constant column height despite any leakage. Competence was measured at pressures of: 0·2, 0·5, 1·0, 2·0, 5·0, 7·5, 10, 15, 20, 25, 50, 75, 100, 150, 200 and 250 cmH_2O. The water column height was measured from the top of the valve cusps. A non-wettable container was placed below the valve to collect any leakage. The volume of water collected was measured with a measuring cylinder capable of measurement to 0·1 ml. To measure the leak rate at each pressure, the valve was exposed to the relevant water column and a timed collection made over 1 min. Valves were also subjected suddenly to these pressures. Sudden pressure exposure was achieved by positioning the valve level with the top of the appropriate water column and applying a tubing clamp to the tube connecting the column to the valve. The valve was then moved to the bottom of the column and the clamp released, rapidly exposing the valve to the full pressure exerted by the column. Valve leakage (mean and standard error) for constant and sudden pressure exposure was calculated from five measurements at each pressure gradient. Analysis of variance was used to demonstrate any difference between leak rates with constant or sudden pressure exposure at each of the pressure gradients where valve incompetence was detected.

Assessment of valve patency and competence in surviving animals

Six valves were constructed and studied in six surviving animals 1 day (2 valves), 5 days, 12 days, 35 days and 112 days (1 valve each) later.

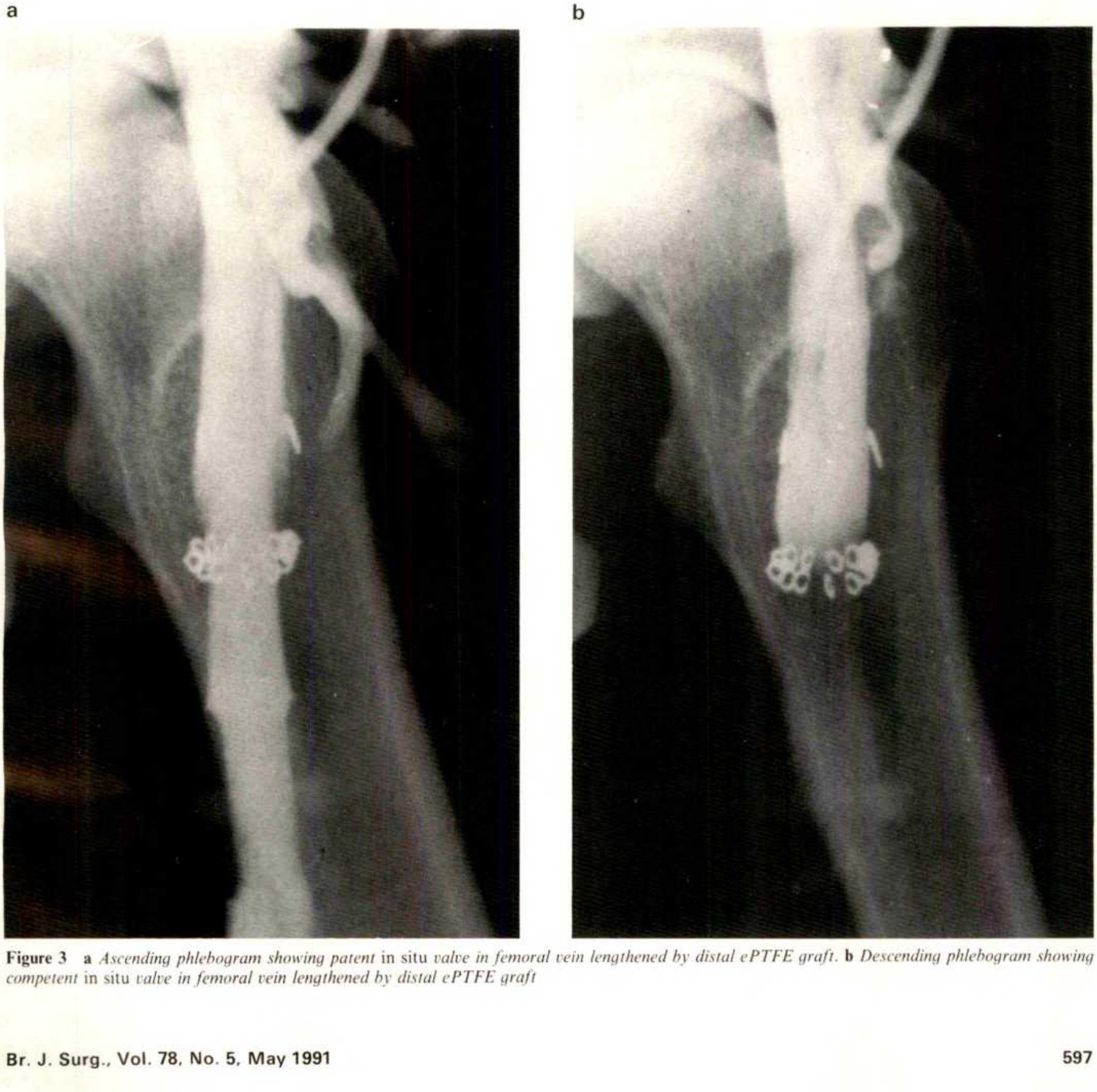

Figure 3 **a** *Ascending phlebogram showing patent* in situ *valve in femoral vein lengthened by distal ePTFE graft.* **b** *Descending phlebogram showing competent* in situ *valve in femoral vein lengthened by distal ePTFE graft*

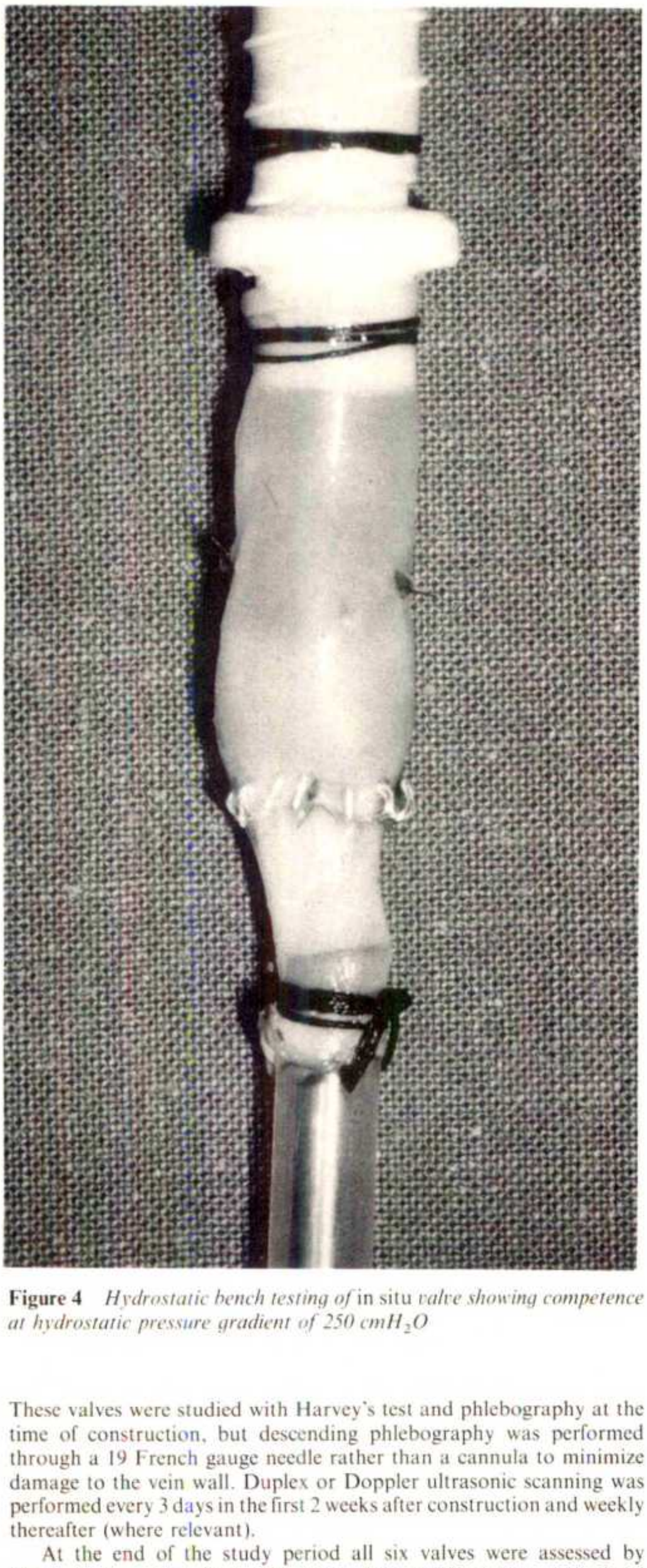

Figure 4 *Hydrostatic bench testing of* in situ *valve showing competence at hydrostatic pressure gradient of 250 cmH$_2$O*

These valves were studied with Harvey's test and phlebography at the time of construction, but descending phlebography was performed through a 19 French gauge needle rather than a cannula to minimize damage to the vein wall. Duplex or Doppler ultrasonic scanning was performed every 3 days in the first 2 weeks after construction and weekly thereafter (where relevant).

At the end of the study period all six valves were assessed by Harvey's test, ascending and descending phlebography and visual examination of the intima. Three valves were then subjected to hydrostatic bench testing and three valves were fixed in 10 per cent formol saline and stained with haematoxylin and eosin for histological examination.

Results

Harvey's test and phlebography

Forty-one valves were constructed in 34 animals. Ascending phlebography showed all 41 valves to be patent and free from gross technical error. All 41 valves were competent when assessed by Harvey's test. At descending phlebography 38 valves were competent, three showing mild reflux (*Table 1*).

Hydrostatic testing

Constant pressure exposure. All 27 valves were tested in the vertical position. Twenty-four valves were fully competent with no leak whatsoever. Three valves showed minor degrees of leakage with maximum leak rates of 1·82 (valve 3), 4·64 (valve 13) and 1·50 (valve 29) ml/min at pressures of 100, 7·5 and 15 cmH$_2$O respectively (*Table 2*). The leak through each of these valves varied depending on the pressure gradient exerted. *Figure 5* shows the relationship between pressure gradient and leak rate (reflux profile) for each of these three valves.

Sudden pressure exposure. The same three valves that leaked with constant pressure exposure (Nos 3, 13 and 29) also leaked with sudden pressure exposure (*Table 2*). There was no significant difference between the leak caused by sustained and sudden pressure.

Valve patency and competence 1–112 days after construction

All six valves constructed in the surviving animals remained patent and free of thrombus as assessed by duplex or Doppler ultrasonic examination before removal. At removal, all six valves were patent at ascending phlebography and five were competent at descending phlebography. One valve, harvested 5 days after construction, showed mild reflux. Static pressure testing was performed on three valves (two valves removed 1 day after construction and one valve removed 12 days after construction). All three valves were fully competent in the range 0·2–250 cmH$_2$O. Visual examination of the intima revealed no disruption or thrombosis in any of the valves. Histological examination of the three valves removed at 5, 35 and 112 days showed no evidence of thrombosis in the sinus or cusp regions (*Figure 6*).

Discussion

The technique of *in situ* valve construction has several potential advantages over other methods of valve replacement; the valve

Table 1 *Summary of valve construction, testing and results*

Valves constructed (*n*)	41
Harvey's test competent	41
Ascending phlebogram patent	41
Descending phlebogram competent	38 (3 valves mild reflux)
Hydrostatic testing (*n*)	27
Full competence	24
Surviving animal valves (*n*)	6
Study interval (days)	1 (2 valves) 5 (1 valve) 12 (1 valve) 35 (1 valve) 112 (1 valve)
Findings at time of harvest (*n*)	
Harvey's test competent	6
Ascending phlebogram patent	6
Descending phlebogram competent	5
Hydrostatic testing (3 valves)	3 valves competent
Macroscopic appearance	6 valves, no thrombosis
Histological appearance (3 valves)	3 valves, no thrombosis

Table 2 *Mean(s.e.m.) maximum leak rates of incompetent valves*

	Maximum leak rate (ml/min)		Hydrostatic pressure gradient (cmH$_2$O)
Valve no.	Sudden	Constant	
3	2·18(0·35)	1·82(0·31)	100
13	4·60(0·13)	4·64(0·16)	7·5
29	1·54(0·03)	1·50(0·03)	15

Sudden and constant refer to method of valve exposure to hydrostatic pressure gradient

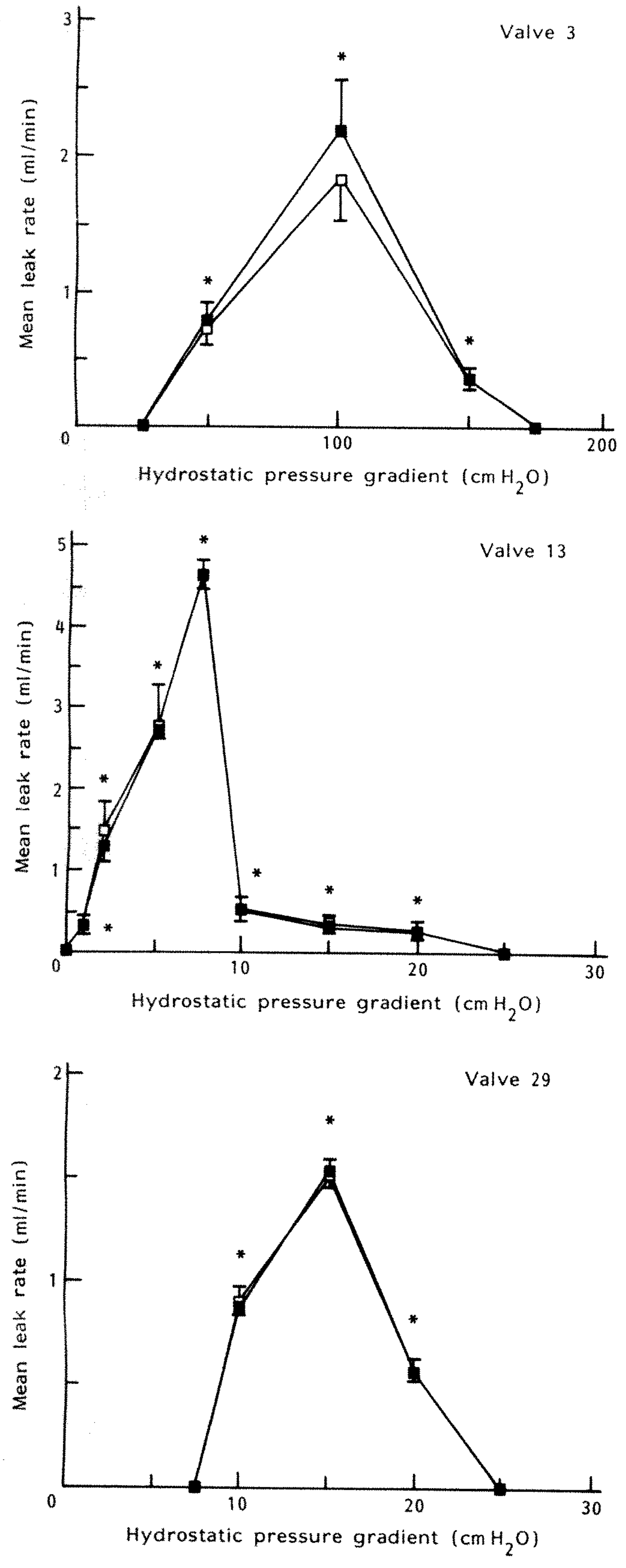

Figure 5 *Reflux profile showing* in situ *valve mean leak rates at varying hydrostatic pressure gradients with constant* (□) *and sudden* (■) *pressure exposure. Bars show s.e.m.* * $P > 0{\cdot}5$

is constructed from autogenous vein wall (eliminating problems of antigenicity), all luminal valve surfaces are native venous endothelium, and the method of construction leaves virtually no intraluminal foreign material. The likelihood of thrombosis is thus reduced to a minimum and is superior to that of homograft, xenograft or prosthetic valves, which have high rates of thrombosis[18–21]. Not only is the material used autogenous, but it is native to the site of valve construction and is thus likely to retain its vascularity. This is thought to be important in avoiding late fibrosis and consequent incompetence, and it may be a factor in the late failure of transplanted valves[24].

The valve is automatically size-matched to the host vein, a rare event with transposed or transplanted valves, which dilate and sometimes become incompetent when placed in veins of disparate diameter[25]. The use of external support to prevent dilatation in transposed or transplanted valves has not been fully examined but initial studies suggest it is unsuccessful[26].

Although the valve is constructed *in situ*, the vein graft necessary to lengthen the vein must be transplanted from a distant site. Nevertheless, short autogenous vein grafts have high patency rates[27,28]. No grafts in surviving animals were affected by thrombosis, athough the number of surviving animals studied was inadequate to draw firm conclusions. In humans, an internal or external jugular vein graft could be used to lengthen the valve-bearing vein. We do not advocate construction of valve mechanisms in transplanted vein as the inherent advantages of *in situ* construction would be lost.

There was no early (within 4 h of valve construction) or late thrombosis in any valve. Harvey's test showed a high degree of early competence, as did descending phlebography and hydrostatic bench testing. Harvey's test appears to be a less sensitive indicator of competence than the other tests, although it has been claimed that the relatively dense contrast media used in descending phlebography may provide an unphysiological challenge to venous valves[29]. Reflux in the three phlebographically incompetent valves was minor and unlikely to be of physiological significance.

Sudden pressure exposure was performed during bench testing to mimick the Valsalva manoeuvre that occurs during coughing or straining. Constant pressure exposure was intended to mimick the prolonged valve challenge of standing or gentle walking. There was no difference in competence or leak rates with sudden or gradual pressure exposure. This suggests a rapid cusp response and that poor cusp apposition was responsible for the leakage observed in three valves. A wide range of pressures was employed, and particular attention was paid to the low values at which valves function physiologically. Valves remained competent at both low and higher, possibly unphysiological, pressures, suggesting that the pressure required to close the cusps was very low ($<0{\cdot}2\,\mathrm{cmH_2O}$). Competence at high pressure indicates that cusp prolapse (which has affected other valve construction methods) did not occur[22,30].

One phlebographically incompetent valve was incompetent at bench testing and two hydrostatically incompetent valves were competent at descending phlebography. This discrepancy was probably caused by the different valve attitudes employed. Valve attitude has been shown in unpublished studies to affect performance. The one phlebographically and hydrostatically incompetent valve contained a small ligated side branch on the edge of one cusp and thereafter every effort was made to avoid including side branches in the intussusception. No explanation was found for the incompetence of the other valves. Of the six valves constructed in surviving animals, five were competent phlebographically, including the valve harvested at 112 days. These initial results are encouraging with respect to the long-term properties of the technique.

The development of a technique in healthy animal veins is far removed from its use in a patient with post-thrombotic disease. However, most patients with post-thrombotic change have a patchy distribution of disease and it should be possible to identify areas of healthy vein suitable for valve construction. To avoid variables that have obscured the results of previous studies[15,31] any such procedures should be undertaken as part of a clinical trial, involving patients with ulcers refractory to conservative treatment and who have previously undergone correction of any superficial and communicating vein reflux.

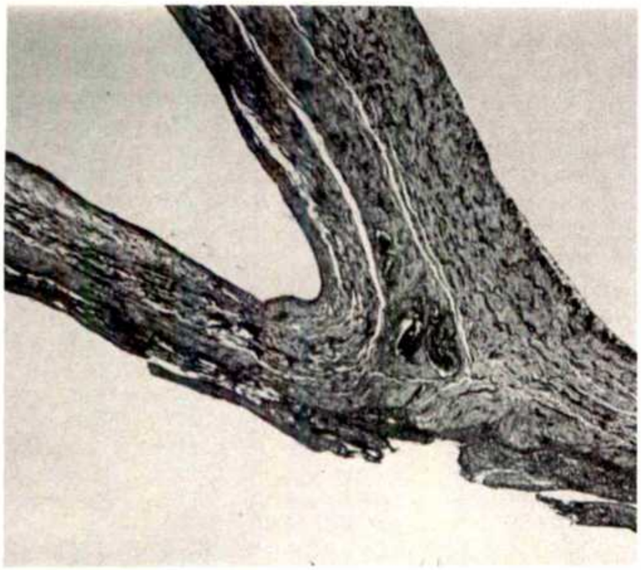

Figure 6 *Longitudinal section of vein showing junction of vein wall and constructed valve cusp 35 days after construction. Original magnification ×40*

Ideally, the profunda femoris vein should be competent[32]. Treatment of calf pump failure by venous reconstruction requires correction of all abnormalities[3]. Before this technique can be used in humans, further studies of hydrodynamic valve function and long-term patency and competence are required and these are currently underway.

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References

1. Callam MJ, Ruckley CV, Harper DR, Dale JJ. Chronic ulceration of the leg: extent of the problem and provision of care. *Br Med J* 1985; **290**: 1855–6.
2. Cornwall JV, Lewis JD. Leg ulcers revisited. *Br J Surg* 1983; **70**: 681.
3. Browse NL, Burnand KG, Lea Thomas M. *Diseases of the Veins*. London: Edward Arnold, 1988.
4. Widmer LK. *Peripheral Venous Disorders. Basle Study III*. Bern: Hans Huber, 1978.
5. Hoare MC, Nicolaides AN, Miles CR *et al.*The role of primary varicose veins in venous ulcerations. *Surgery* 1982; **92**: 450–3.
6. Sethia KK, Darke SG. Long saphenous incompetence as a cause of venous ulceration. *Br J Surg* 1984; **71**: 754–5.
7. Burnand K, O'Donnell T, Lea Thomas M, Browse NL. Relation between postphlebitic changes in the deep veins and the results of surgical treatment of venous ulcers. *Lancet* 1976; **i**: 936–8.
8. Raju S. Venous insufficiency of the lower limb and stasis ulceration. *Ann Surg* 1983; **197**: 688–97.
9. Kistner RL. Primary venous valve incompetence of the leg. *Am J Surg* 1980; **140**: 218–24.
10. Eriksson I, Almgren B. Surgical reconstruction of incompetent deep vein valves. *Up J Med Sci* 1988; **93**: 139–43.
11. Kistner RL. Surgical repair of a venous valve. *Straub Clin Proc* 1968; **34**: 41–3.
12. Hallberg D. A method for repairing incompetent valves in deep veins. *Acta Chir Scand* 1972; **138**: 143–5.
13. Jones JW, Elliot F, Kerstein MD. Triangular venous valvuloplasty. *Arch Surg* 1982; **117**: 1250–1.
14. Jessup G, Lane RJ. Repair of incompetent venous valves: a new technique. *J Vasc Surg* 1988; **8**: 569–75.
15. Kistner RL, Sparkuhl MD. Surgery in acute and chronic venous disease. *Surgery* 1979; **85**: 31–41.
16. Taheri SA, Lazar L, Elias SM, Marchand P. Vein valve transplant. *Surgery* 1982; **91**: 28–33.
17. Eiseman B, Malette W. An operative technique for the construction of venous valves. *Surg Gynecol Obstet* 1953; **97**: 731–4.
18. Kaya M, Grogan JB, Lentz D, Tew W, Raju S. Glutaraldehyde-preserved venous valve transplantation in the dog. *J Surg Research* 1988; **45**: 294–7.
19. Hill R, Schmidt S, Evancho M, Hunter T, Hillegass D, Sharp W. Development of a prosthetic venous valve. *J Biomed Mater Res* 1985; **19**: 827–32.
20. Taheri SA, Rigan D, Wels P, Mentzer R, Shores RM. Experimental prosthetic vein valve. *Am J Surg* 1988; **156**: 111–14.
21. Phifer TJ, Rohr MS. The pathogenesis of leaflet failure in prosthetic venous valves. *Phlebology* 1988; **3**: 115–21.
22. Rosenbloom MS, Schuler JJ, Bishara RA, Ronan SG, Flanigan DP. Early experimental experience with a surgically created totally autogenous venous valve: a preliminary report. *J Vasc Surg* 1988; **7**: 642–6.
23. Harvey W. *Exercitatio Anatomica de Motu Cordis et Sanguini in Animalibus*. Frankfurt: W Fitzer, 1628.
24. Taheri SA, Shores R. Successful use of sutureless prosthetic vein valves in dog. *Proc 10ème Congress Mondial Union Internationale de Phlebologie*. Strasbourg: John Libby, 1989: 1035–7.
25. Nash T. Long term results of vein valve transplants placed in the popliteal vein for intractable post-phlebitic venous ulcers and pre-ulcer skin changes. *J Cardiovasc Surg* 1988; **29**: 712–16.
26. Raju S, Fredericks R. Valve reconstruction procedures for nonobstructive venous insufficiency: rationale, techniques and results in 107 procedures with two- to eight-year follow-up. *J Vasc Surg* 1988; **7**: 301–10.
27. Haimovici H, Zinicola N, Noorani M, Hoffert PW. Vein grafts in the venous system. *Arch Surg* 1963; **87**: 542–7.
28. Wright CB, Hobson RW, Swan KG. Autografts and homografts in canine femoral venous reconstruction: a double-blind study. *Surgery* 1973; **74**: 654–9.
29. Lea Thomas M, Keeling FP, Ackroyd JS. Descending phlebography: a comparison of three methods and an assessment of the normal range of deep vein reflux. *J Cardiovasc Surg* 1986; **27**: 27–30.
30. Spiegowski M, Ziólkowski P, Przetakiewicz Z, Polanski J. Reconstruction of the venous valves. *Proc 10ème Congress Mondial Union Internationale de Phlebologie*. Strasbourg: John Libby, 1989: 1032–4.
31. Taheri SA, Prendergast DR, Lazar E *et al.* Vein valve transplantation. *Am J Surg* 1985; **150**: 201–2.
32. Eriksson I, Almgren B. Influence of the profunda femoris vein on venous hemodynamics of the limb. *J Vasc Surg* 1986; **4**: 390–5.

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Five-year vascular audit from a district hospital

Vascular patients under the care of one surgeon over a 5-year period have been reviewed, from computer-based discharge records, with regard to in-hospital measures of outcome to determine whether or not surgery was being performed to an acceptable standard. Out of 466 procedures, 30 per cent of patients had at least one complication, 14 per cent had further surgery and 9 per cent died. Outcome was examined within the following treatment groups: aorto/iliac aneurysm, aortofemoral bypass, femoroproximal popliteal bypass, femorodistal popliteal bypass, femorocrural bypass, embolectomy and percutaneous transluminal angioplasty. Patients having below-knee bypass surgery were found to have an unacceptably high rate of complications, reoperations and amputations. An overall rate of reoperation for postoperative bleeding of 5 per cent was also considered to be high. With these exceptions, it was concluded that the surgery was being performed to an acceptable standard, but that comparative audit of this type remained difficult while there was a deficiency of national statistics against which the work of individual surgeons could be judged.

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The author, a general surgeon with a vascular interest, was appointed to develop the vascular service in a district hospital where previously the only arterial operations had been for ruptured aortic aneurysm. Information on all admissions has been maintained on computer and, after 5 years, it seemed appropriate to examine the vascular work with regard to in-hospital measures of outcome, to see whether the surgery was being carried out to an acceptable standard.

Patients and methods

Patient discharge summaries were prepared using a standard form from which the information was entered on a desk-top computer by a personal secretary. Software was developed in dBaseII (Ashton Tate, Jefferson City, California, USA) which printed a summary and then stored the information for later audit[1]. All admissions, commencing in late 1984, were entered on computer, including in-patients and day-cases for both general and vascular surgery. The information presented in this paper represents an audit of the vascular patients for the 5 years from January 1985 to December 1989, obtained by interrogating the computer. Because the computer database was not designed specifically for vascular patients, no information was stored on the indications for surgery or type of graft. These additional data for the lower limb bypass operations were extracted from the medical records.

Patients with intermittent claudication were selected for angiography only if they were thought to be not smoking and had symptoms severely restricting activity, in general a walking distance of less than 100 m. Patients were then allotted to percutaneous transluminal angioplasty (PTA) or bypass surgery on the basis of the angiographic findings. In most instances the need to take a bypass graft below the knee was considered a contraindication to surgery for intermittent claudication. Individuals with critical ischaemia (rest pain, gangrene or ulcer, or a combination of these) were admitted for urgent angiography and treatment on the next operating list. Chemical sympathectomy was used for critical ischaemia in patients considered unsuitable for a bypass graft, either on clinical grounds or when the angiogram failed to show a vessel suitable for grafting. All patients having a synthetic graft were given intravenous antibiotics which were commenced at operation and continued for 24 h. Intraoperative heparin was given routinely to all patients having femorodistal bypass, but not to those having aortic grafts. After operation patients were given subcutaneous heparin until fully ambulant. Aspirin, 300 mg daily, was prescribed for patients with synthetic grafts to the popliteal artery.

Lower limb bypass surgery was divided into four groups: aortofemoral, femoroproximal popliteal, femorodistal popliteal and femorocrural. The other main patient groups were aorto/iliac aneurysm, embolectomy, PTA and major amputation (above and below the knee). Amputations were further subdivided into primary and secondary depending on whether or not the patient had had an earlier procedure.

In order to allow for comparison with outcome from other publications presenting similar mixed data, the determinants of success or failure were similar to those published by the Canadian Vascular Society[2] and the Vascular Registry in Southern Sweden (VRISS)[3]. These were: complications, further operations, major amputations (above and below the knee) and deaths. Complications were further subdivided into general and surgical. Because some patients had more than one complication or second operation, a figure was given for the total number of patients in whom a complication or reoperation was recorded and then details were given of all complications and further operations within each treatment group. Graft infection and thrombosis were not fully accounted for within the main groups and so these complications were detailed separately, as were those patients having further surgery for bleeding.

Results

All patients (Table 1)

The total number of patient admissions to the unit during the 5 years under review was 6723; thus the 738 vascular admissions represented 11 per cent of the total. A third of all vascular admissions were emergencies. Of the vascular operations, 30 per cent were associated with at least one complication, 14 per cent had further surgery and there was an operative mortality rate of 9 per cent. Bypass grafts accounted for 44 per cent of the procedures. The other large patient groups

Table 1 *Vascular patient numbers, admission type and vascular operations for the 5 years 1985–89*

	n
Total no. of vascular admissions	738
No. of individual patients	477
Emergency/elective admissions	228/510 (31/69)
Vascular operations	466
Emergency/elective	171/295 (37/63)
Patients with complications	141 (30)
Reoperations	65 (14)
Operative deaths	44 (9)
Grafts	203 (44)

Values in parentheses are percentages

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Table 2 *In-hospital outcome for the main treatment groups for the 5 years 1985–89*

	Aorto/iliac aneurysm	Aortofemoral bypass	Femoroproximal popliteal bypass	Femorodistal popliteal bypass	Femorocrural bypass	Embolectomy	Transluminal angioplasty
Number	59	32	38	16	5	33	57
Emergency/elective admission	20/39	2/30	6/32	4/12	3/2	33/0	7/50
Patients with complications	22	5	13	12	5	15	5
Further operations	7	3	5	7	5	9	5
Major amputation	1	0	1	3	3	2	1
Deaths	9	0	0	1	1	9	0
Complications							
General							
Cardiac arrest						1	
Cardiac failure	2		1				
Chest infection	5	1					
Hypotension	1						
Myocardial infarction						1	
Renal failure	5						
Respiratory failure	3					3	
Surgical							
Femoral embolus	1						
Graft infection			1		2		
Graft thrombosis		1	2	2	1		
Lymphatic leak	1	3	2				
Intestinal obstruction	1						
Ischaemia/gangrene leg	4	1		3		11	1
Paralytic ileus	2						
Skin necrosis					1		
Swelling leg	1		2	5			
Postoperative haemorrhage	3	1	3	2	4	2	1
Wound haematoma			1				3
Wound infection	1		5	3	2	2	
Further operations							
Amputation (above knee)	1		1	2	3	2	1
Amputation (below knee)				1	1		
Amputation foot				2			
Amputation toe				1			1
Axillofemoral bypass						1	
Embolectomy	2					5	
Femorofemoral cross-over		1				1	
Femoropopliteal bypass							1
Graft thrombectomy		1	1				
Laparotomy for adhesions		1					
Prostatectomy						1	
Re-exploration wound	5	1	3	2	4	2	1
Removal graft			1				
Repair artery						1	
Sympathectomy (chemical)							1

were: chemical sympathectomy (15 per cent), PTA (12 per cent), primary amputation (11 per cent) and embolectomy (7 per cent).

Aorto/iliac aneurysm (Table 2)

Two-thirds of these aneurysm patients were admitted electively, 12 per cent required further surgery, 2 per cent (one patient) had an amputation and 15 per cent died. Six of the deaths were in emergency and three in elective admissions, giving mortality rates of 30 per cent and 8 per cent respectively. The most frequent general complication was major organ failure (cardiac, respiratory and renal); the most frequent surgical complications were distal ischaemia and bleeding, for which two patients had an embolectomy and five had the abdomen re-explored respectively, but only three of these latter patients were found to be bleeding at the second operation.

Aortofemoral bypass (Table 2)

This group included 25 aortobifemoral, two aortounifemoral, two aortobi-iliac and three iliofemoral bypasses. Twenty-six operations were for intermittent claudication and six were for critical ischaemia. All grafts were of woven Dacron® (E. I. du Pont, Wilmington, Delaware, USA). Most patients were admitted electively and there were no amputations or deaths.

Femoroproximal popliteal bypass (Table 2)

Information concerning symptoms and type of graft could only be obtained for 35 of the 38 operations. Seventeen operations

Table 3 *Graft infection, graft thrombosis and postoperative bleeding for the 5 years 1985–89*

Patient no.	Operation	Graft	Timing	Site of bleeding	Comment
Graft infection					
1	Femoral aneurysm	Dacron	Same admission		Graft removed
2	Axillofemoral	Dacron	Same admission		Graft removed, AKA, died
3	Axillofemoral	Dacron	Same admission		Graft removed
4	Femorofemoral cross-over	Dacron	Same admission		Graft removed, AKA
5	Femoroproximal popliteal	Dacron	Same admission		Graft removed, femoropopliteal bypass 6/12 later
6	Femorocrural	*In situ* vein	Same admission		Graft ligated, AKA, died
7	Femorocrural	*In situ* vein	Same admission		Graft ligated, AKA
8	Aortofemoral	Dacron	32/12		Graft removed, AKA
Graft thrombosis					
1	Femorodistal popliteal	PTFE	Same admission		AKA
2	Femorodistal popliteal	*In situ* vein	Same admission		AKA
3	Femorocrural	*In situ* vein	Same admission		BKA revised to AKA
4	Femoroproximal popliteal	Dacron	Same admission		Thrombectomy
5	Femoroproximal popliteal	Biograft	Same admission		AKA
6	Femoroproximal popliteal	PTFE	24/12		Femoropopliteal bypass
7	Femoroproximal popliteal	PTFE	13/12		BKA revised to AKA
8	Femoroproximal popliteal	Dacron	9/12		Thrombectomy
9	Iliopopliteal	PTFE	10/52		AKA
10	Femorofemoral cross-over	Dacron	10/52		Thrombectomy
11	Subclavian artery	Reversed vein	3/52		Thrombectomy
Postoperative bleeding					
Primary (early)					
1	Aortic aneurysm	Dacron	Same day	Wound	
2	Aortic aneurysm	Dacron	Same day	Wound	
3	Aortic aneurysm	Dacron	Same day	Wound	
4	Aortofemoral	Dacron	Same day	Wound	Groin lymphatic leak
5	Femoroproximal popliteal	Dacron	Same day	Wound	
6	Femoroproximal popliteal	Dacron	Same day	Wound	
7	Femoroproximal popliteal	*In situ* vein	Same day	Graft	
8	Femorodistal popliteal	*In situ* vein	Same day	Wound	
9	Femorocrural	*In situ* vein	Same day	Wound	
10	Femorocrural	*In situ* vein	Same day	Wound	
11	Iliopopliteal	PTFE	Same day	Wound	
12	Angioplasty		Same day	Arterial puncture	
13	Embolectomy		Same day	Arteriotomy	
14	Embolectomy		Same day	Arteriotomy	Died
15*	Femorocrural	*In situ* vein	Same day	Anastomosis	
16	Femorodistal popliteal	*In situ* vein	2/7	Wound	Wound infection, graft safe
Secondary (delayed)					
15*	Femorocrural	*In situ* vein	16/7 and 25/7	Graft	Graft infection, repaired, ligated, AKA
17	Femorocrural	*In situ* vein	26/7	Anastomosis	Graft infection, ligated, AKA, died
18	Axillofemoral popliteal	PTFE	43/7	Wound	No graft infection

* Patient no. 15 had both primary and secondary wound haemorrhage; AKA, above-knee amputation; BKA, below-knee amputation; PTFE, polytetrafluoroethylene

were for intermittent claudication and 18 were for critical ischaemia. There were 21 woven Dacron, seven polytetrafluoroethylene (PTFE), six *in situ* vein and one umbilical vein bypasses. The majority of patients were admitted electively. All the complications were surgical, most frequently wound infection or postoperative wound haemorrhage. This latter complication was the reason for half of the additional operations. One patient with a wound infection subsequently developed a graft infection.

Femorodistal popliteal bypass (Table 2)

All but two of the 16 patients had surgery for critical ischaemia. There were 11 *in situ* vein and five PTFE bypasses. Three-quarters of patients were admitted electively and most had at least one complication. Seven required further surgery, two for bleeding. One patient died.

Femorocrural bypass (Table 2)

All patients had critical ischaemia. There were three femoroanterior and two femoroposterior tibial *in situ* vein grafts. All patients had major complications and all underwent further surgery. Four grafts were complicated by haemorrhage, one graft on three separate occasions. Three patients came to above-knee amputation.

Embolectomy (Table 2)

All 33 patients were admitted as emergencies, five with upper limb emboli. Further surgery was performed on 27 per cent and a similar proportion died. Nearly half had at least one complication; these were a combination of both general and surgical, the most frequent being continued ischaemia of the leg.

Transluminal angioplasty (Table 2)

Most patients were admitted electively and many of these were second admissions following earlier angiography. In eight patients the lesion could not be crossed by a guide-wire, a technical failure rate of 14 per cent. Five patients had a further procedure, one for bleeding from the groin puncture site.

Graft infection, graft thrombosis and postoperative bleeding (Table 3)

There were eight (4 per cent) graft infections among the 203 bypasses. Three of these were in extra-anatomic bypasses and two were in vein grafts to the distal tibial vessels; one patient presented acutely nearly 3 years after an aortofemoral bypass with bleeding from one groin. Of the 11 thromboses, five occurred in hospital and most were in grafts to the popliteal or tibial vessels. When amputation was necessary as a consequence of infection or thrombosis, all patients eventually had an above-knee amputation.

Eighteen (4 per cent) patients had a haemorrhage requiring re-exploration after 466 operations (5 per cent when chemical sympathectomies were excluded). The majority had primary would haemorrhage occurring within 48 h of surgery. Of note, six (38 per cent) of the 16 infrageniculate *in situ* vein bypasses were complicated by early wound haemorrhage. Three patients had secondary reactionary bleeding. Two of these were in vein bypasses which had become infected, one of which had already had a primary bleed. Both patients lost their limbs. The third patient was readmitted 43 days after an axillopopliteal bypass with bleeding from the knee wound which was found to be from a small artery in the wound; there was no graft infection.

Table 4 *Amputations for the 5 years 1985–89*

	n	Previous procedure
Below-knee	56	
Primary	43 (77)	
Secondary	13 (23)	5 chemical sympathectomy 3 failed grafts 2 exploration calf vessels 2 amputation toe 1 transluminal angioplasty
Died	8 (14)	
Above-knee	34	
Primary	8 (24)	
Secondary	26 (76)	13 below-knee amputations 13 failed grafts
Died	6 (18)	

Values in parentheses are percentages

Amputations (Table 4)

Of the below-knee procedures, 23 per cent were secondary following earlier unsuccessful surgery, whereas 76 per cent of the above-knee amputations followed failed surgery, either below-knee amputation or bypass graft.

Other procedures

Seventy patients had a chemical sympathectomy; 33 attended as day-cases. No follow-up information was available for the day-cases, but five in-patients had a below-knee and two had an above-knee amputation.

There were 16 lower limb bypasses in addition to those detailed above. Eleven used Dacron grafts from the aorta to one or both popliteal arteries (seven for intermittent claudication and four for critical ischaemia) and five were PTFE iliopopliteal grafts (two for intermittent claudication and three for critical ischaemia). Of these 16 grafts one was re-explored for postoperative bleeding; there were no major amputations or deaths.

Seventeen extra-anatomic bypasses were performed: seven femorofemoral, six axillofemoral and four femoropopliteal cross-over. Information was available on symptoms and graft materials for only 15 patients. Two had surgery for intermittent claudication and 13 for critical ischaemia. There were seven Dacron and eight PTFE grafts. Eight patients had complications (three graft infections), three had secondary operations (one above-knee amputation) and three died.

Comparison with expected outcome (Table 5)

Outcome for aorto/iliac aneurysm and aortofemoral bypass surgery compares favourably with expected figures derived from the literature, although a slightly higher reoperation rate in the

Table 5 *Comparison between percentage outcome presented in this paper (actual) and that to be expected from the literature*

	Complications	Further operations	Amputation	Death
Overall				
Actual	32	14		9
Expected		11[3]		8[3]
Aorto/iliac aneurysm				
Actual	37	12	2	15
Expected	12–64[2–4]	5–9[3–5]	<1–5[2–4]	10–25[2,3,5–8]
Aortofemoral bypass				
Actual	16	9	0	0
Expected	7[2]		1–2[2,9,10]	2–5[2,9,11]
Femoroproximal popliteal bypass				
Actual	34	13	3	0
Expected	7–10[12,13]	6[13]	2[13]	3[13]
Femorodistal popliteal bypass				
Actual	75	44	19	6
Expected	14[12]	12[14]		4–6[15,16]
Femorocrural bypass				
Actual	100	100	60	20
Expected	24–46[2,12]	20[14]	3–12[2,17–20]	2–16[17,21–24]
Embolectomy				
Actual	45	27	6	27
Expected	30–40[3]	22[3]	18–19[3,25]	26–27[3,25]
Transluminal angioplasty				
Actual	9	9	2	0
Expected	2–18[26–29]	2–5[27–30]	<1[30]	<1[27,30]
Below-knee amputation				
Actual				14
Expected				9–10[31]
Above-knee amputation				
Actual				18
Expected				28[31]

aneurysm group and a higher rate of complications in the bypass group were noted. In the emergency aneurysm group the mortality rate of 30 per cent compares well with published figures of 31–51 per cent[2,4–8], as does the elective mortality rate of 8 per cent with an expected rate of 3–9 per cent[2,5–8]. Of particular note in the femoroproximal popliteal bypasses was the high rate of reoperation (13 *versus* 6 per cent). The below-knee bypasses were associated with a considerably higher than expected rate of complications, further surgery and amputation. For embolectomies no ready figure was available for complication rates, but the information from the VRISS[3] suggests that this is likely to be in the order of 30–40 per cent. We recorded more complications, but had similar rates of reoperation and mortality with a low rate of amputation (6 *versus* 18–19 per cent). PTA compared favourably, with the apparent exception of reoperations, but the expected 2–5 per cent of further operations were only for bleeding and this compared favourably with our rate of 2 per cent for this complication. Published figures for unsuccessful PTA vary from 10 to 20 per cent[26,27,30]; again, this compared favourably with our figure of 14 per cent.

Discussion

In summarizing these results it has not been possible to provide a comparative figure for overall complications from the literature. The only source of information concerning overall outcome for vascular practice, combining teaching and district hospitals, for a large population comes from the VRISS[3], which did not state how many patients had a recorded complication. However, we have recorded high numbers of complications within the present operative groups. This, to some extent, may be explained by the high number of emergency patients compared with the Swedish experience (37 *versus* 30 per cent). Furthermore, the method of data collection will have tended to favour the recording of most patient events, since discharge summaries were usually prepared within a few days of the patient leaving hospital.

There was a high overall reoperation rate compared with the VRISS[3] data, and within individual groups this was more than would have been anticipated. Reoperation for bleeding was the commonest reason for further surgery and at 5 per cent was higher than the expected 3–4 per cent[32]. Greater vigilance will be needed to reduce this figure.

The incidence of graft infection is reported as 1–6 per cent[33,34]. The present figure of 4 per cent was thus acceptable.

Bypass grafts below the knee produced poor results. The problems identified were those that could be anticipated in patients with severely ischaemic limbs having prolonged operations with extensive wounds and long grafts, namely bleeding, infection and thrombosis. These operations were done mainly in the last 2 years of the study period and it is felt that there was a learning curve associated with this surgery. Most papers concerning these procedures come from centres dedicated to performing large numbers of these operations. Data from general vascular practice in district hospitals is lacking. It is of interest to note that the collective experience from Canada[2] yielded an amputation rate of 12 per cent which, although better than that recorded here, was considerably worse than that reported by some authors[20,24]. Despite these comments it is felt that our results were not acceptable and will have to be improved if femorocrural surgery is to be continued. In particular, greater vigilance must be exercised when closing wounds and consideration must be given to routine antibiotic prophylaxis. Up to now antibiotics have been given only to patients having synthetic grafts.

Vascular surgery with its high level of complications, including some specific in-hospital determinants of outcome, presents a ready area for audit. Although there is pressure from both the Royal College of Surgeons of England[35] and from the Government[36] for clinical audit to be formalized, a major difficulty in preparing this paper was the absence of guidelines about how this should be done. Figures giving expected outcomes from British hospitals do not yet exist and some form of regional or national data collection must be undertaken to establish values against which individual surgeons may assess their own results. The results presented here might provide a framework around which such data collection could take place.

The information presented in this paper was not checked by reference to hospital records. However, all summaries were prepared by the author and checked before the printed copy was filed. Thus the consistency of the data will have been maintained at the stage of summary preparation. A few errors were found in the computer database when patient notes were being examined to obtain information on symptoms and graft types, but they did not materially alter the results. If this type of audit of large patient numbers is to prove useful, the accuracy of computer databases will have to be accepted, since the numbers involved precludes retrieval of information from hospital records.

In conclusion, the author considers that he is performing vascular surgery to an acceptable standard in most areas, but an effort must be made to reduce the frequency of reoperation for bleeding and to improve the outcome for patients having long distal bypasses. A major difficulty exists with this type of audit in that the data against which an individual surgeon's results can be checked is very inadequate.

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References

1. Holdsworth JD. Surgical audit using dBase II. In: Coleridge Smith PD, Scurr JH, eds. *Microcomputers in Medicine*. London: Springer-Verlag, 1988: 31–41.
2. Sladen JG. Morbidity audit, 1984. Canadian Society for Vascular Surgery. *Can J Surg* 1987; **1**: 3–4.
3. Vascular Registry in Southern Sweden. Vascular Registry in Southern Sweden – the first year experience of a Vascular Registry. *Eur J Vasc Surg* 1989; **3**: 563–9.
4. Fielding JWL, Black J, Ashton F, Slaney G. Ruptured aortic aneurysms: postoperative complications and their aetiology. *Br J Surg* 1984; **71**: 487–91.
5. Amundsen S, Trippestad A, Viste A, Soreide O. Abdominal aortic aneurysms – a national multicentre study. *Eur J Vasc Surg* 1987; **1**: 239–43.
6. Campbell WB, Collin J, Morris PJ. The mortality of abdominal aortic aneurysm. *Ann R Coll Surg Engl* 1986; **68**: 275–8.
7. Castleden WM, Mercer JC, and the members of the West Australian Vascular Service. Abdominal aortic aneurysm in Western Australia: descriptive epidemiology and patterns of rupture. *Br J Surg* 1985; **72**: 109–12.
8. Christenson J, Eklof B, Gustafson I. Abdominal aortic aneurysms: should they all be resected? *Br J Surg* 1977; **64**: 767–72.
9. King RB, Myers KA, Scott DF, Devine TJ. Aortio-iliac reconstructions for intermittent claudication. *Br J Surg* 1982; **69**: 169–72.
10. Brewster DC. Aorto-iliac occlusive disease. In: Bell P, Tilney NL, eds. *Vascular Surgery*. London: Butterworths, 1984: 78–107.
11. Brewster DC. Aortoiliac, aortofemoral, and iliofemoral arteriosclerotic occlusive disease. In: Haimovici H, ed. *Vascular Surgery*. Norwalk: Appleton and Lange, 1989: 455–73.
12. Anderson LI, Neilsen OM, Buchardt Hansen HJ. Umbilical vein bypass in patients with severe lower limb ischaemia: a report of 121 consecutive cases. *Surgery* 1985; **97**: 294–8.
13. King BR, Myers KA, Scott DF, Devine TJ, Johnson N, Morris PJ. Femoropopliteal vein grafts for intermittent claudication. *Br J Surg* 1980; **67**: 489–92.
14. Dardik H. Limb salvage procedures of the lower extremities. In: Bell PRF, Tilney NL, eds. *Vascular Surgery*. London: Butterworths, 1984: 108–22.
15. Dardik H. The glutaraldehyde stabilized umbilical vein graft: experience with lower extremity revascularization. In: Pollock JG, McKay AJ, Eastcott HHG, eds. *Topical Reviews in Vascular Surgery*. Bristol: Wright PSG, 1982 63–81.

16. Clifford PC, Gazzard V, Lawrance RJ, Clyne CAC, Webster JHH. Below knee femoropopliteal bypass in severe ischaemia: results using EXS Dacron and human umbilical vein. *Ann R Coll Surg Engl* 1986; **68**: 319–21.
17. Baumann G. Der femoro-crurale Bypass. Erfahrungen mit der ringverstarkten PTFE-Prothese (Gore-Tex). *Angio* 1983; **5**: 277–80.
18. Gannon MX, Goldman MD, Simms MH, Ruddock S, Ashton F, Slaney G. Perioperative complications of *in-situ* vein bypass. *Ann R Coll Surg Engl* 1986; **68**: 134–6.
19. Harling H, Lorentzen JE, Nielsen OM, Buchardt Hansen HJ. Femoro-distal bypass – a worthwhile procedure? *Eur J Vasc Surg* 1987; **1**: 133–5.
20. Szilagyi DE, Hageman JH, Smith RF, Elliott JP, Brown F, Dietz P. Autogenous vein grafting in femoropopliteal athero-sclerosis: the limits of its effectiveness. *Surgery* 1979; **86**: 836–51.
21. Harris PL, Campbell H. Femoro-distal bypass for critical ischaemia: is the use of prosthetic grafts justified? *Ann Vasc Surg* 1986; **1**: 66–72.
22. McLoughlin R, O'Leary G, Fitzgerald LP, O'Donnell JA. The effect of distal anastomotic site on PTFE graft patency in lower extremity bypass. *Eur J Vasc Surg* 1989; **3**: 417–19.
23. Robison JG, Brewster DC, Abbott WM, Darling RC. Femoropopliteal and tibioperoneal artery reconstruction using human umbilical vein. *Arch Surg* 1983; **118**: 1039–42.
24. Veith FJ, Gupta SK, Ascer E. Small artery bypasses to the tibial and peroneal arteries for limb salvage. In: Haimovici H, ed. *Vascular Surgery*. Norwalk: Appleton and Lange, 1989: 501–16.
25. Dregelid EB, Stangeland LB, Eide GE, Trippestad A. Patient survival and limb prognosis after arterial embolectomy. *Eur J Vasc Surg* 1987; **1**: 263–71.
26. Harrington DP. Percutaneous transluminal angioplasty: a review. In: Bell P, Tilney NL, eds. *Vascular Surgery*. London: Butterworths, 1984: 145–74.
27. Howd A, Loose H, Chamberlain J, Proud G. Lower limb angioplasty: a review of 300 procedures. *Br J Surg* 1987; **74**: 327.
28. Katzen BT. Percutaneous transluminal angioplasty in peripheral vascular disease. In: Haimovici H, ed. *Vascular Surgery*. Norwalk: Appleton and Lange, 1989: 302–9.
29. Murie JA. Percutaneous transluminal angioplasty and vascular surgery for lower limb ischaemia. *Br J Surg* 1988; **75**: 1051–2.
30. Fraedrich G, Beck A, Bonzel T, Schlosser V. Acute surgical intervention for complications of percutaneous transluminal angioplasty. *Eur J Vasc Surg* 1987; **1**: 197–203.
31. Sethia KK, Berry AR, Morrison JD, Collin J, Murie JA, Morris PJ. Changing pattern of lower limb amputation for vascular disease. *Br J Surg* 1986; **73**: 701–3.
32. Bergqvist D, Ljungstrom K-G. Haemorrhagic complications resulting in reoperation after peripheral vascular surgery: a fourteen-year experience. *Vasc Surg* 1987; **6**: 134–8.
33. Earnshaw JJ. Prevention of infection after vascular reconstruction. *J Antimicrob Chemother* 1989; **23**: 480–3.
34. Goldstone J. Infected prosthetic arterial grafts. In: Haimovici H, ed. *Vascular Surgery*. Norwalk: Appleton and Lange, 1989: 564–74.
35. Royal College of Surgeons of England. *Guidelines to Clinical Audit in Surgical Practice*. London: Royal College of Surgeons of England, 1989.
36. Government White Paper. *Working for Patients. Medical Audit: Working Paper 6*. London: Her Majesty's Stationery Office, 1989.

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Vasodilatory capacity of the skin in venous disease and its relationship to transcutaneous oxygen tension

Low transcutaneous oxygen tension (P_{tc,O_2}) *values in the supramalleolar skin of patients with venous disease are often reported. This measurement involves heating the skin to 43°C to cause maximum vasodilatation and is valid only if liposclerotic and normal skin can vasodilate to the same degree. Forty-four limbs were studied, 15 with lipodermatosclerosis (LDS), 14 with uncomplicated varicose veins, and 15 controls. A* P_{tc,O_2} *electrode was modified to incorporate a laser Doppler probe. Laser Doppler flux was measured in the supramalleolar skin before and after local heating to 43°C and the relative increase in flux was measured. The* P_{tc,O_2} *was then measured at the same site and on the chest. Vasodilatory capacity was expressed as the ratio of peak:basal laser Doppler flow, and the* P_{tc,O_2} *was expressed as a leg:chest ratio. Median laser Doppler flow was higher in limbs with LDS (median 67 mV) than in normal limbs (median 40 mV)* ($P < 0{\cdot}03$). P_{tc,O_2} *was higher in control limbs (median ratio 0·94) than in limbs with LDS (median 0·53)* ($P < 0{\cdot}006$)*. The microcirculation in LDS had less capacity to vasodilate after heating (median factor of increase 5·4) than normal skin (median factor of increase 12·3)* ($P < 0{\cdot}001$)*. A simple regression analysis was performed on all pairs of data, and revealed a correlation between* P_{tc,O_2} *and vasodilatory capacity* ($r = 0{\cdot}524$, $P < 0{\cdot}001$)*. The results indicate that low* P_{tc,O_2} *levels in venous disease reflect an inability of the microcirculation to increase its flow in response to local heating; inferences about the oxygen content of liposclerotic skin at normal temperatures cannot be drawn using this technique.*

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It is widely believed that skin damage in chronic venous insufficiency is the result of tissue hypoxia. This belief stems largely from the concept of an oxygen diffusion barrier in liposclerotic skin, which is thought to be the result of pericapillary fibrin deposition[1]. The evidence for this is derived from transcutaneous oximetry. Studies in patients with lipodermatosclerosis (LDS) have regularly demonstrated that transcutaneous oxygen tension (P_{tc,O_2}) is reduced in skin damaged by venous hypertension[2–5]. However, the method of operation of the oximeter involves heating the skin to a temperature of 43–44°C to cause maximal vasodilatation and facilitate oxygen measurement. Workers at the Royal Free Hospital in London have demonstrated that at 37°C, P_{tc,O_2} in skin affected by venous disease does not appear to differ from normal, and may indeed be higher in liposclerotic skin[6].

P_{tc,O_2} readings depend on vasodilatation produced by hyperthermia[7], so it might be expected that an impairment of vasodilatory capacity would lead to reduced P_{tc,O_2} values without necessarily reflecting reduced oxygen levels in the tissue under normal conditions. The aim of this study was to investigate precisely what aspect of skin function is measured when using transcutaneous oximetry in venous disease, by measuring both the hyperaemic response to heating and P_{tc,O_2} in liposclerotic and normal skin.

Patients and methods

Forty-four limbs have been studied. These were divided into three groups: 15 normal controls with neither venous nor peripheral arterial disease, 14 limbs with uncomplicated varicose veins, and 15 limbs with clinical LDS, with or without active ulceration. Patients with LDS were assessed by photoplethysmography and duplex scanning, performed by an experienced operator on an Acuson 128 scanner (Acuson Incorporated, Mountain View, California, USA), to confirm venous insufficiency as the cause of skin damage. The precise venous diagnoses for these patients are shown in *Table 1*. Age and sex data for the three groups are displayed in *Table 2*.

All studies were performed in an environment-controlled chamber at an ambient temperature of 22°C and a relative humidity of 30 per cent, with the patient in a supine position. All skin measurements were performed on skin 6 cm above the medial malleolus when skin changes were absent, and on the area of deepest pigmentation in limbs with LDS.

Patients lay supine for an acclimatization period of at least 15 min. Laser Doppler flux was then measured using a Periflux PF2 laser Doppler velocimeter (Perimed, Stockholm, Sweden). Calibration was performed using Periflux Motility Standard PF100 solution (Perimed). The laser Doppler probe was mounted eccentrically in a specially constructed collar which incorporated a heating element and temperature sensing thermistors (*Figure 1*), similar to that used by Rayman *et al.* in diabetic patients[8]. When a resting trace had been collected, the heater was switched on. Over a period of 10–15 min this heated the brass block within the collar to 43°C, the same temperature at which P_{tc,O_2} measurements are made. When laser Doppler flux had reached a maximum, the collar was rotated through 45° eight times, and the flux was recorded in each new area of skin. The mean of the eight values was then taken as the peak flux. The purpose of this manoeuvre was to obviate the possibility of uneven skin heating leading to a falsely low flux in any one position. Peak laser Doppler flow was expressed as a ratio of maximum flow after heating to baseline flow recorded beforehand.

P_{tc,O_2} was then measured on the same skin using a standard oximeter (Kontron, Frankfurt, Germany). The P_{tc,O_2} was also recorded on the

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Table 1 *Venous diagnosis in 15 patients with chronic venous insufficiency and skin changes*

	LDS alone	LDS + healed ulcer	LDS + active ulcer	Total
DVI	1	1	2	4
DVI + SVI	1	0	4	5
SVI + incompetent perforators	1	1	0	2
Isolated SVI	1	2	1	4

LDS, lipodermatosclerosis; DVI, deep venous insufficiency; SVI, superficial venous insufficiency

Table 2 *Age and sex characteristics of study groups*

	Sex distribution, M:F	Mean age, years
Controls	4:11	53 (25–76)
Varicose veins	5:9	55 (24–78)
Lipodermatosclerosis + ulcers	10:5	62 (31–79)

Ranges are given in parentheses

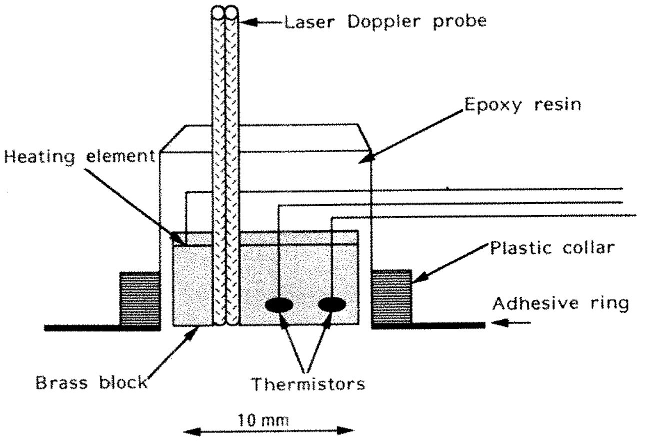

Figure 1 *Laser Doppler mount incorporating heating element and thermistors to sense the temperature*

anterior chest wall and results were expressed as a ratio of the leg:chest P_{tc,O_2}.

Data were analysed using medians and interquartile ranges (IQRs) as descriptors and the Mann–Whitney *U* test for intergroup comparisons, as they did not follow a Gaussian distribution.

Results

Basal laser Doppler flow was significantly higher in skin affected by LDS than in normal skin or skin of patients with varicose veins (*Figure 2*). Median flow in the LDS patients was 67 mV (IQR 49–113) compared with 40 mV (IQR 40–57) in controls ($P<0.01$) and 47 mV (IQR 35–60) in patients with varicose veins ($P<0.03$).

P_{tc,O_2} values were lower in liposclerotic skin than in the other two groups (*Figure 3*). In patients with LDS, the median leg:chest ratio was 0·53 (IQR 0·25–0·72), while in patients with varicose veins it was 1·01 (IQR 0·85–1·15) ($P<0.002$) and in controls it was 0·94 (IQR 0·72–1·21) ($P<0.006$). The difference between controls and patients with uncomplicated varicose veins was not significant. P_{tc,O_2} in the clinically normal skin of limbs affected elsewhere by LDS did not differ from normal values (median value 0·97, IQR 0·8–1·25) and was significantly higher than the liposclerotic skin on the same leg ($P<0.002$).

The ratio of peak laser Doppler flow after heating to preheating flow was also significantly lower in the LDS group (*Figure 4*). The median ratio in this group was 5·4 (IQR 2·25–6·5), while in controls it was 12·3 (IQR 7·5–16·1) ($P<0.003$) and in the varicose vein group it was 11·0 (IQR 6·3–14·4) ($P<0.02$). The latter two groups did not differ significantly. The median ratio in apparently normal skin in

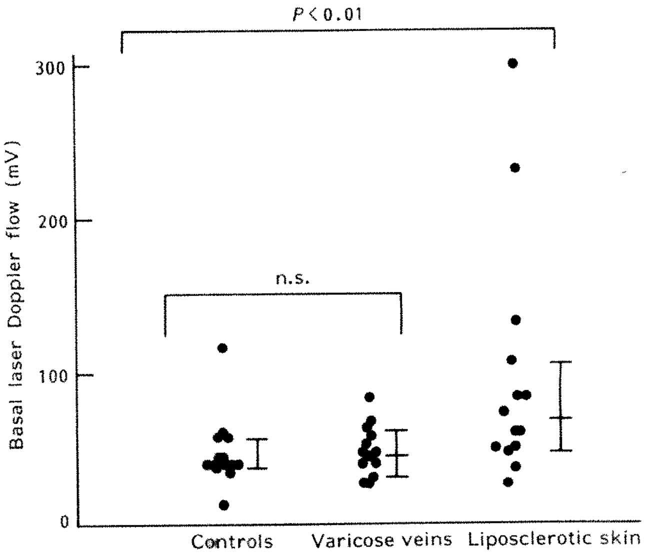

Figure 2 *Basal laser Doppler flux (mV) in the three study groups. ns, not significant. Bars represent interquartile range*

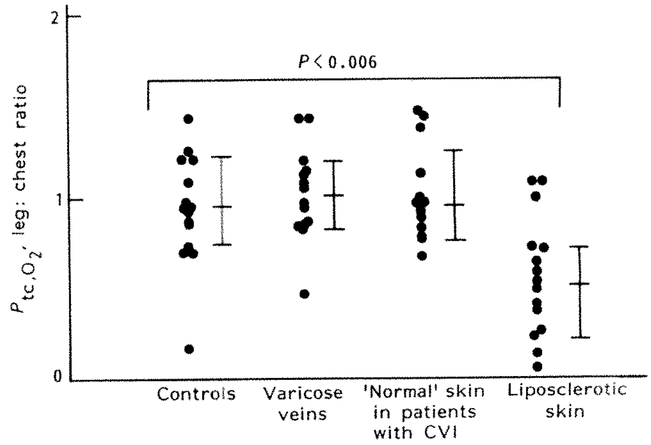

Figure 3 *Transcutaneous oxygen tension ratios for skin of controls, skin affected by varicose veins, 'normal' skin in patients with chronic venous insufficiency (CVI), and in skin with lipodermatosclerosis. Bars represent interquartile range*

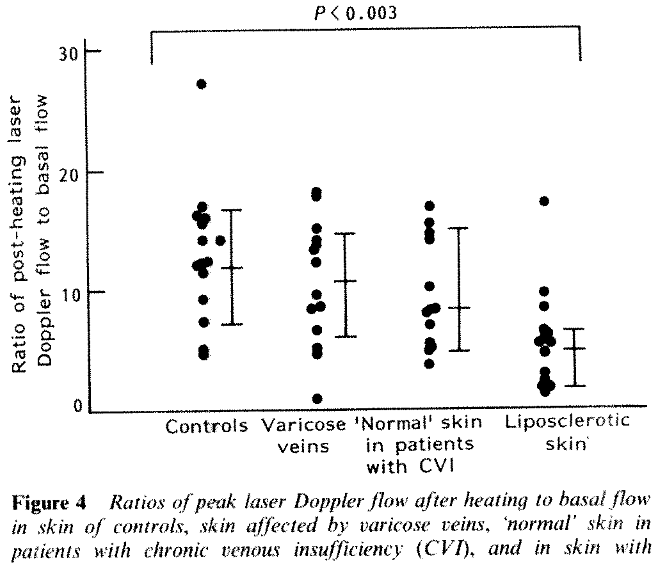

Figure 4 *Ratios of peak laser Doppler flow after heating to basal flow in skin of controls, skin affected by varicose veins, 'normal' skin in patients with chronic venous insufficiency (CVI), and in skin with lipodermatosclerosis. Bars represent interquartile range*

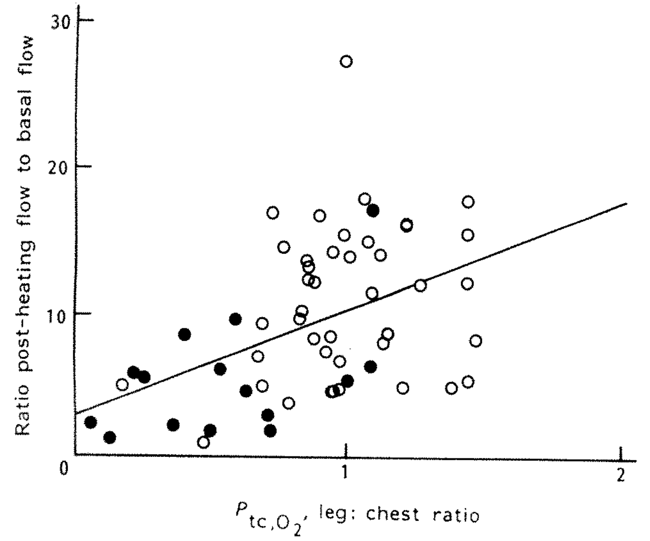

Figure 5 *Relationship between* P_{tc,O_2} *and peak blood flow after heating. The regression line has been fitted to all data* ($r=0·524$). ●, *Patients with lipodermatosclerosis;* ○, *normal skin*

the limbs with LDS was 8·3 (IQR 5·2–14·4); this was significantly different from liposclerotic skin ($P<0·03$) but not from skin of controls or skin of patients with simple varicose veins.

Because basal flow was higher in limbs with LDS than others, it was important to establish that the reduced ratio was not merely a function of a higher denominator; absolute peak flows for the four groups were therefore compared. This confirmed the differences; median peak flow in the LDS group was 353 mV (IQR 193–457), which differed significantly from that of controls (median flow 587 mV, IQR 403–697, $P<0·03$) and of the normal skin of the same limb (median flow 658 mV, IQR 327–780, $P<0·04$). A significant difference could not, however, be demonstrated between limbs with LDS and limbs with varicose veins for this parameter; the median peak flow in the latter was 507 mV (IQR 329–575) ($P>0·05<0·1$).

A simple regression line was calculated for all paired values of P_{tc,O_2} and 'vasodilatability', as reflected by the before and after heating flow ratios. This revealed a firm correlation between the two parameters ($r=0·524$, $P<0·001$) (*Figure 5*).

Discussion

Laser Doppler velocimetry is now well established as the principal non-invasive method for investigating skin blood flow. It correlates well with xenon-133 clearance and with thermographic methods[9,10]. It has also been used in conjunction with capillary microscopy, with comparable results[11]. Absolute measurements of blood flow are not feasible, but appropriate calibration allows comparison between different subjects by comparing laser Doppler flux.

The present findings of a reduced P_{tc,O_2} in skin damaged by venous hypertension are in agreement with those of other workers[2–5]. There is a broad overlap between normal values, and those in the disease group, again a common finding and one which presumably explains the failure of some studies to show a significant difference between the groups[12,13].

The finding of a reduced vasodilatory capacity in LDS in response to local heating is hitherto unreported. It was previously known that the responsiveness of liposclerotic skin to a short period of arterial occlusion was reduced in comparison with that in normal skin[14], but this had not been extended to other forms of microcirculatory stimulation. The present study, by its nature, is unable to elicit the cause of this phenomenon; however, speculation is possible based on current theories of venous skin damage. It should be noted that in this study, measurements were taken with the patient supine; the situation with the limb dependent, in which position arteriolar constriction would be expected, has yet to be defined.

Several possibilities exist to explain the reduced vasodilatory capacity in LDS. Fibrin, which has been shown by Burnand *et al.*[15] to form pericapillary cuffs in venous disease, may exercise some form of mechanical restriction on the capacity of the smallest vessels to increase their diameter. This mechanism could operate in a manner similar to that seen in diabetics, in whom increased minimal vascular resistance in the skin of the leg due to arteriolar hyalinosis has been demonstrated using an isotope washout technique[16]. Such mechanical restriction could operate only under conditions that would normally cause hyperaemia, since resting skin blood flow is actually higher in LDS than in normal skin.

If a sympathetic neuropathy occurred in venous disease, it would be conceivable that a 'capillary steal' phenomenon was present of the sort described in diabetics by Wollersheim *et al.*[17]. This model proposes that sympathetic dysfunction leads to increased total flow through the dermis, but, by opening the arteriovenous shunts in the lower regions of the dermis, to a net decrease in nutritive blood flow through the papillae. It is clear from this study and from the work of Belcaro[18] that an increased total flow is present in liposclerotic skin. However, there is no evidence that a sympathetic neuropathy exists in chronic venous disease, although the subject has not been widely studied.

A more likely explanation is an increased peripheral resistance to flow in the skin vessels in venous disease. This may be mediated by occlusion of skin capillaries by white blood cells and by endothelial cell activation[19]. Scott *et al.* have demonstrated that white cells become rapidly sequestered in the normal upper limb in response to raised venous pressure[20]. The site of sequestration has yet to be identified, but because it is known that decreased shear stress leads to increased leucocyte/endothelial cell adhesion[21], it is likely that this occurs in the postcapillary venules. This would lead to an effective reduction in luminal diameter and a resultant increase in resistance to flow. Cytokines (such as interleukin 1) released from monocytes would have the effect of causing endothelial cell oedema and increased expression of intercellular adhesion molecules[22] with further reduction in luminal cross-sectional area. Electron microscopy has demonstrated marked endothelial cell oedema in liposclerotic skin, with frequent cytoplasmic protrusions into the lumen[23]. Interleukin 1 has also been demonstrated to cause the release of von Willebrand factor from human endothelial cells[24]; this may help to explain the microthrombosis and patchy flow through liposclerotic skin found by Haselbach *et al.*[25].

Transcutaneous oximetry is dependent on arterial pressure; this has been shown both in normal subjects and in patients with peripheral vascular disease[26,27]. Similarly, in normal subjects, the P_{tc,O_2} has been shown to be linearly related to skin blood flow as measured by xenon-133 clearance when local heating is applied[28]. The results of this study show a firm relationship between the capacity of the skin to increase its blood flow in response to heat and transcutaneous oximetry values. Because heating the skin to 43°C is an integral part of P_{tc,O_2} measurement, this implies that the technique is dependent on a normal vasodilatory capacity. When this is not present, as in liposclerotic skin, no inferences can be drawn about the oxygenation of the skin at normal temperatures. We conclude that transcutaneous oximetry may be useful as a marker of severity of skin damage in venous disease, but only in as far as the hyperaemic stimulus reveals a perfusion defect. The evidence from Dodd *et al.*[6] suggests that it is only under hyperaemic conditions that the perfusion defect becomes apparent and that P_{tc,O_2} is in fact normal in LDS when measured without the induction of hyperaemia. This, in conjunction with the findings reported here, suggests that oxygen levels may be normal in liposclerotic skin and that the cause of skin damage should be sought elsewhere.

References

1. Browse NL, Burnand KG. The cause of venous ulceration. *Lancet* 1982; **ii**: 243–5.
2. Clyne CAC, Ramsden WH, Chant ADB, Webster JHH. Oxygen tension on the skin of the gaiter area of limbs with venous disease. *Br J Surg* 1985; **72**: 644–7.
3. Kolari PJ, Pekanmaki K, Pohjola RT. Transcutaneous oxygen tension in patients with post-thrombotic leg ulcers: treatment with intermittent pneumatic compression. *Cardiovasc Res* 1988; **22**: 138–41.
4. Mannarino E, Pasqualini L, Maragoni G, Sanchini R, Regni O, Innocente S. Chronic venous incompetence and transcutaneous oxygen pressure: a controlled study. *Vasa* 1988; **17**(3): 159–61.
5. Mani R, White JE, Barrett DF, Weaver PW. Tissue oxygenation, venous ulcers and fibrin cuffs. *J R Soc Med* 1989; **82**: 345–6.
6. Dodd HJ, Gaylarde PM, Sarkany I. Skin oxygen tension in venous insufficiency of the lower leg. *J R Soc Med* 1985; **78**: 373–6.
7. Huch A, Huch R. A new method for arterial blood sampling in newborn infants and adults. *Arch Dis Child* 1973; **48**: 982.
8. Rayman G, Wiliams SA, Spencer PD, Smaje LH, Wise PH, Tooke JE. Impaired microvascular hyperaemic responses to minor skin trauma in type I diabetes. *Br Med J* 1986; **292**: 1295–8.
9. Holloway GA, Watkins DW. Laser Doppler measurement of cutaneous blood flow. *J Invest Dermatol* 1977; **69**: 306–9.
10. Nilsson GE, Tenland T, Oberg PA. Evaluation of a laser Doppler flowmeter for measurement of tissue blood flow. *IEEE Trans Biomed Eng* 1980; **27**: 597–604.
11. Tooke JE, Ostergren J, Fagrell B. Synchronous assessment of human skin microcirculation with laser Doppler flowmetry and dynamic capillaroscopy. *Int J Microcirc Clin Exp* 1983; **2**: 277–84.
12. Quigley FG, Faris IB. Transcutaneous oxygen potentials in venous disease. *Aust NZ J Surg* 1989; **59**: 165–8.
13. Belcaro G, Rulo A, Vasdekis S, Williams MA, Nicolaides AN. Combined evaluation of post-phlebitic limbs by laser doppler flowmetry and transcutaneous $P\mathrm{O}_2/P\mathrm{CO}_2$ measurements. *Vasa* 1988; **17**: 257–61.
14. Tanner R, Cherry GW, Hale C, Ryan TJ. Impaired hyperaemic response in the microcirculation in patients with venous leg ulcers. *Br J Dermatol* 1989; **121**(Suppl 34): 45.
15. Burnand KG, Whimster I, Naidoo A, Browse NL. Pericapillary fibrin in the ulcer-bearing skin of the leg: the cause of lipodermatosclerosis and venous ulceration. *Br Med J* 1982; **285**: 1071–2.
16. Kastrup J, Norgaard T, Parving HH, Lassen NA. Increased minimal vascular resistance and arteriolar hyalinosis in skin on the leg in insulin-dependent diabetic patients. *Scand J Clin Lab Invest* 1987; **47**: 475–82.
17. Wollersheim H, Netten PM, Lutterman JA, Lenders JWM. Ephedrine improves microcirculation in the diabetic neuropathic foot. *Angiology* 1989; **40**: 1030–4.
18. Belcaro G. Microvascular evaluation by laser-Doppler flowmetry of the effects of Centellase in the treatment of severe venous hypertension and leg ulcers. *Phlebology* 1987; **2**: 189–95.
19. Coleridge Smith PD, Thomas P, Scurr JH, Dormandy JA. Causes of venous ulceration: a new hypothesis. *Br Med J* 1988; **296**: 1726–7.
20. Scott HJ, McMullin GM, Coleridge Smith PD, Scurr JH. Venous ulceration: the role of the white blood cell. *Phlebology* 1989; **4**: 153–9.
21. Lawrence MB, McIntire LV, Eskin SG. Effect of flow on polymorphonuclear leukocyte/endothelial cell adhesion. *Blood* 1987; **70**: 1284–90.
22. Prober JS. Cytokine-mediated activation of vascular endothelium. *Am J Pathol* 1988; **133**: 426–33.
23. Wenner A, Leu HJ, Spycher M, Brunner U. Ultrastructural changes of capillaries in chronic venous insufficiency. *Exp Cell Biol* 1980; **48**: 1–14.
24. Schorer AE, Moldow CF, Rick ME. Interleukin 1 or endotoxin increases the release of von Willebrand factor from human endothelial cells. *Br J Haematol* 1987; **67**: 193–7.
25. Haselbach P, Vollenweider U, Moneta G, Bollinger A. Microangiopathy in severe chronic venous insufficiency evaluated by fluorescence video-microscopy. *Phlebology* 1986; **1**: 159–69.
26. Eickhoff JH, Ishihara S, Jacobsen E. Effect of arterial and venous pressures on transcutaneous oxygen tension. *Scand J Clin Lab Invest* 1980; **40**: 755–60.
27. Allen PIM, Goldman M. Skin blood flow: a comparison of transcutaneous oximetry and laser Doppler flowmetry. *Eur J Vasc Surg* 1987; **1**: 315–18.
28. Eickhoff JH, Jacobsen E. Correlation of transcutaneous oxygen tension to blood flow in heated skin. *Scand J Clin Lab Invest* 1980; **40**: 761–5.

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Comparison of duplex ultrasonography and venography in the diagnosis of deep venous thrombosis

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Sixty-five patients with suspected deep venous thrombosis (DVT) in 68 limbs were entered consecutively into a study to compare venography with duplex ultrasonography scanning. Both tests were performed on 64 limbs, venography being contraindicated in four. Overall, duplex scanning correctly identified 86 per cent of DVTs diagnosed on venography and correctly excluded 80 per cent with negative venograms. Nearly all errors arose in the diagnosis of calf DVT. In the femoral vein duplex scanning had a specificity of 100 per cent and a sensitivity of 95 per cent. In addition, duplex scanning provided data on the limb not undergoing venography. Of 55 limbs that underwent bilateral duplex scanning, five had thrombus in the femoropopliteal segment and a negative contralateral venogram. In addition, three Baker's cysts were diagnosed. Duplex scanning can be used in patients in whom venography is contraindicated and may also provide information about the contralateral limb. We regard femoropopliteal duplex scanning as sufficiently accurate that treatment can be initiated on the basis of the scan. Duplex scanning should replace venography as the standard method of diagnosing femoropopliteal DVT; radiographic studies should now be required only when the scan result is in doubt.

It is widely recognized that patients with thrombosis in the femoral vein with extension into the iliac system are at major risk of developing pulmonary embolism and have a significant incidence of the postphlebitic syndrome.

Venography has been the 'gold standard' diagnostic test for deep venous thrombosis (DVT) for more than a quarter of a century. With a co-operative patient and an experienced radiologist, the test has proved both reliable and accurate. However, venography is invasive, expensive, and subject to a number of potential problems. A minority of patients are not able to have venography, either because they are not fit to be moved to the radiology department or because of allergy to radiological contrast materials. In addition venous cannulation may be difficult or contraindicated and the study may prove to be unsatisfactory for a variety of technical reasons. Even with an experienced radiology team, a number of authors have shown that up to 25 per cent of patients requiring venography may be either unable to have the test or may have an uninterpretable study[1,2]. Venography may also cause thrombosis in previously normal veins in a small proportion of individuals[3]. There is, therefore, a need for a less invasive but equally reliable investigation. The additional advantage of a non-invasive test would be the opportunity to perform repeat studies to monitor the response to treatment.

There are a number of alternative non-invasive diagnostic tests available, such as thermography, fibrinogen uptake scanning, plethysmography, Doppler measurement of flow, and identification of thrombus in major veins using ultrasonography. The last two modalities may be combined as the so-called 'duplex' scanner.

This study was undertaken to assess the accuracy of duplex ultrasonography in diagnosing femoral vein thrombosis and to compare it with venography. The opportunity was also taken to compare the two techniques in the diagnosis of venous thrombosis of the calf veins.

Patients and methods

A consecutive series of 65 patients was studied. Patients were entered into the study by the referring physician on the suspicion of DVT. Patients underwent both venography and duplex scanning within 24 h. The staff performing each test were unaware of the results of the other investigation.

Venography was carried out using a standard protocol[4]. In the semierect position with the leg under examination non-weight bearing and a tourniquet around the ankle, between 50 and 70 ml of low osmolar radiological contrast medium was injected into a dorsal foot vein. Three views were taken of the calf and two views of the popliteal vein. After this the patient was gradually lowered into the supine position and views of the femoral and iliac veins were obtained. Further views were taken as necessary. Following completion of the examination, the venous system was flushed clear with physiological saline and this was checked fluoroscopically.

All venograms were reported 'blind' by a single consultant radiologist (I.B.N.) for the presence or absence of thrombus in the calf, popliteal, femoral or iliac veins according to the criteria of Williams[5]. If the result was equivocal, the films were re-examined after an interval of 2 weeks and regraded. This final report was used for the eventual analysis.

Duplex scanning was performed using a 5 MHz linear array transducer (Acuson, Mountain View, California, USA) coupled to an Acuson 128 scanner. The femoral veins were imaged with the patient supine, and the popliteal veins with the patient sitting. If the patient was unable to sit up, the popliteal fossa was scanned with the patient in the lateral position or prone. The following features were specifically sought in all patients: (1) a clear lumen with no filling defects; (2) compressibility by gentle probe pressure (imaged in transverse section); (3) a normal spontaneous phasic flow with respiration; (4) flow surge on calf compression; (5) no reflux on calf release; and (6) normal valve cusp movement (when identified).

Duplex scans were reported by the scanning technician at the time of scanning on a specially designed pro forma. Thrombus was graded as present or absent in the calf, popliteal or femoral veins. Proximal extension of thrombus into the external iliac vein was assessed routinely, but consistent images of the common iliac vein proved difficult and

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Table 1 *Sensitivity, specificity and accuracy of duplex scanning compared with venography. Results by segment of venous system studied*

Thrombus site	Venogram +ve	Duplex +ve	Duplex sensitivity (%)	Duplex specificity (%)	Diagnostic accuracy (%)
Femoral	22	21	95	100	96
Popliteal	23	21	91	83 (98)	74 (89)
Calf	21	17	81	89	70

Figures in parentheses are those obtained following review of the popliteal duplex scans

findings at this level have not been included in the results. If thrombus was identified, it was further classified into occlusive or non-occlusive, depending on whether any flow signal could be obtained from the involved vein. Scans were recorded on to videotape and kept for subsequent review. The initial report was used for comparison with venography.

Results

There were no contraindications to duplex scanning, but four of the 68 limbs did not undergo venography. This was due to failure of vein canalization in two cases and to contrast allergy in one case. In the fourth case venography was contraindicated by severe arterial disease with digital sepsis. All four limbs had negative duplex scans and the patients were not anticoagulated, with no adverse sequelae.

In the remaining 64 limbs, both venogram and duplex results were available. Overall there were 29 positive venograms out of 64 examinations (45 per cent), and duplex scanning correctly identified 25 giving an overall sensitivity of 86 per cent. Of the 35 negative venograms, duplex scanning identified 28 correctly giving a specificity of 80 per cent. Most of the errors were due to interpretation of calf and popliteal thrombosis (*Table 1*). If duplex scanning was compared with venography for all except isolated calf thrombosis it identified 23 of 24 positive venograms (sensitivity 96 per cent) and 28 of 33 negative venograms (specificity 85 per cent), giving a diagnostic accuracy of 81 per cent.

The accuracy of duplex scanning was also examined segment by segment (*Table 2*). In the femoral segment, duplex identified 21 of 22 positive venograms (95 per cent) and all 42 negative venograms (100 per cent). The solitary error was in a patient with popliteal and distal femoral thrombosis extending just proximal to the adductor hiatus. The duplex scan correctly identified the popliteal thrombosis, but missed the thrombus in the lower femoral vein.

Iliac extension of femoral DVT was routinely sought and was identified by duplex scanning in all cases diagnosed venographically. In no case did the thrombus extend further than the distal external iliac vein.

In the popliteal segment, accuracy was lower, with duplex scan identifying 21 of 23 positive venograms (91 per cent) and 34 of 41 negative venograms (83 per cent). Review of the scans identified slow flow and the appearance of clumps of rolling cells (which we term 'rouleaux') as the predominant cause of false positive diagnosis. The other cause of false positive diagnosis was difficulty in compressng the vein behind a swollen knee. These errors were partly due to the learning curve in interpreting duplex findings. We found that few of these errors occurred towards the end of the study.

Blind review of these scans was carried out at the end of the study and resulted in the regrading of six out of the seven initially positive duplex scans as negative due to rouleaux behind the knee, giving a revised sensitivity of 91 per cent and a revised specificity of 98 per cent.

Analysis of the accuracy of calf duplex scanning is more difficult. We did not routinely examine the calf if thrombus was detected in the femoral or popliteal segments. There were 49 limbs in which the calf vessels were examined by both venography and duplex scan. Duplex scan correctly identified 17 of 21 positive venograms (81 per cent) and 25 of 28 negative venograms (89 per cent).

Table 2 *Numbers of limbs with positive or negative studies by venous segment studied*

	Duplex +ve		Duplex −ve	
	Venogram +ve	Venogram −ve	Venogram +ve	Venogram −ve
Femoral	21	0	1	42
Popliteal	21	7 (1)	2	34 (40)
Calf	17	3	4	25

Figures in parentheses are those obtained following review of the popliteal duplex scans

Duplex scanning provided the diagnosis of Baker's cyst in three limbs thought to have a DVT on clinical grounds. This demonstrates that duplex scanning can detect pathology simulating DVT which cannot be diagnosed by venography.

Duplex scanning was also carried out on the non-involved limb in 55 patients. In five limbs (9 per cent), a DVT was diagnosed (three femoropopliteal and two popliteal) in the presence of a negative venogram.

In nine patients the venogram was considered to be less than ideal, due to underfilling of calf veins in four instances and poor opacification of the popliteal vein in one. In the remaining four, the study was inconclusive in one or more vein segments. Although this did not prevent a report being made, this may represent a source of inaccuracy in the venogram data.

Discussion

The variety of tests reported in the literature illustrate that, so far, no single test has proved superior to venography. The main limitations are accuracy and the availability of experienced staff to apply the tests in a reproducible manner.

Thermography seeks to diagnose DVT by detecting a rise in temperature in association with the thrombosed vein segment. The recent introduction of portable equipment using liquid crystals has opened the way for more widespread application of the technique[6,7]. It has a number of major limitations, the most important being that it is not applicable to individuals who have suffered trauma to their lower limbs, or who have significant peripheral vascular disease. This limits its application in high risk groups such as patients undergoing joint replacement.

Radiolabelled fibrinogen scanning has an established place in the detection of DVT. The labelled fibrinogen is incorporated into developing clot and therefore has to be given before the development of the thrombus. This technique is useful for screening, but unsuited to diagnosing established DVT. When used to screen, there is a tendency to overdiagnose[8], especially in the calf. The accuracy of this method decreases in the thigh and it will not readily detect non-occlusive thrombi[9]. Coupled with this, fibrinogen is obtained from pooled plasma which makes it both expensive and a potential infection risk.

Tests that indirectly measure altered flow, such as impedance plethysmography, while good at excluding thrombi, are of variable sensitivity and require considerable experience to obtain reproducible results[10,11]. A disadvantage is that calf thrombi are not readily detected, but, more importantly, non-occlusive thrombi in the proximal veins may also be overlooked.

Ultrasonography is able to recognize occlusive thrombi by detecting non-compressible veins and it has been used to improve the selection of cases for venography[12]. A high degree of accuracy has been demonstrated using compression[12-14] but most studies avoided assessment of the iliac or calf veins. When calf veins are included, the accuracy of the test fell[15,16]. The hand-held Doppler flow probe can also be used to test for DVT, but is of limited accuracy because it cannot detect non-occlusive thrombosis and has difficulty in picking up signals from the smaller calf veins[17].

The combination of B-mode scanning and Doppler shift data from the duplex scanner have advanced the accuracy of these tests in the few series reported to date[12,16,18], although Cronan *et al.*[12] concluded that Doppler analysis improved confidence in the result of ultrasound compression studies rather than the accuracy of diagnosis of DVT. Most studies have concentrated on diagnosis in the femoropopliteal segment.

In the absence of proximal thrombosis, calf vein thrombosis should be excluded by direct examination. Treatment may not need to be started in the face of isolated calf vein thrombosis, but as propagation may occur in up to 10 per cent[19] of cases, the condition should be followed with repeat examinations.

There are a number of important points which emerge from this study. In common with other groups, we have found that diagnostic accuracy is lowest in the calf and that calf vein thrombus was not invariably present when the duplex identified more proximal thrombosis. Isolated calf vein thrombosis is difficult to detect, but the specificity of scanning in the calf allows a high level of confidence in a negative scan which identifies normal veins.

Initial assessment of the popliteal fossa yielded a number of false positive results, most of which occurred early in the study. Blind review of the scans was undertaken some weeks after the study closed to try to identify errors in scan interpretation. Review of the scans reveals that most of the false positive diagnoses were made in patients with sluggish flow and clumping of cells. With increasing experience improved quality of diagnosis can be expected. The other feature of note was that compression of the vein was found to be difficult on a few occasions. This may be related to our technique of examining the patient in the sitting position. One group[10] has commented that this can make it difficult to collapse the popliteal vein with probe pressure.

In the femoral segment accuracy was high, the one error being a patient who had limited extension of thrombus from the popliteal into the distal femoral vein. The scan had correctly identified the popliteal thrombus. Scanning in the region of the adductor hiatus is known to be a source of inaccuracy as it is difficult to visualize the vein over a few centimetres at this level. Increasing experience and improved technique have allowed us to improve our visualization of this area, although isolated thrombus at this location would be one instance of proximal thrombosis where error might be expected.

In summary, we have demonstrated that duplex scanning can identify DVT with a high degree of accuracy in the proximal venous tree of the lower limb. Diagnostic accuracy is lower as one proceeds distally, a factor that should be remembered when interpreting the results of duplex scanning. Isolated calf thromboses are not associated with an adverse outcome unless they propagate. Further study of the ability of duplex scanning to detect such thromboses is warranted to define the optimum diagnostic parameters and to assess the rate of propagation. At present we feel that if reliance is to be placed on duplex scanning, a negative scan should be repeated after an interval of 2 or 3 days. We believe that the duplex scanner has an important role to play in the diagnosis of DVT, and it is our policy to exclude major vein thrombosis with duplex scanning. The use of the duplex scanner should reduce the requirement for venography. It should also allow more accurate follow-up and assessment of the response to treatment, as well as providing alternative diagnoses and information on the opposite limb. Venography is required when the scan result is doubtful and clinical suspicion is strong.

References

1. Hull RD, Hirsch J, Carter CJ *et al.* Diagnostic efficacy of impedance plethysmography for clinically suspected deep-vein thrombosis. A randomized trial. *Ann Intern Med* 1985; **102**: 21–8.
2. Huisman MV, Buller HR, ten Cate JW, Vreeken J. Serial impedance plethysmography for suspected deep vein thrombosis in outpatients. *N Engl J Med* 1986; **314**: 823–8.
3. Bettmann MA, Robbins A, Braun SD, Wetzner S, Dunnick NR, Finkelstein J. Contrast venography of the leg: diagnostic efficacy, tolerance, and complication rates with ionic and nonionic contrast media. *Radiology* 1987; **165**: 113–16.
4. Lea-Thomas M. Phlebography. *Arch Surg* 1972; **104**: 145–51.
5. Williams WJ. Venography. *Circulation* 1973; **47**: 220–1.
6. Sandler DA, Martin JF. Liquid crystal thermography as a screening test for deep-vein thrombosis. *Lancet* 1985; **i**: 665–8.
7. Thomas EA, Cobby MJD, Rhys Davies E, Jeans WD, Whicher JT. Liquid crystal thermography and C reactive protein in the detection of deep vein thrombosis. *Br Med J* 1989; **299**: 951–2.
8. Covey TH, Sherman L, Baue AE. Low dose heparin in postoperative patients. A prospective coded study. *Arch Surg* 1975; **110**: 1021–5.
9. White RH, McGahan JP, Daschbach MM, Hartling RP. Diagnosis of deep-vein thrombosis using duplex ultrasound. *Ann Intern Med* 1989; **111**: 297–304.
10. Hull RD, van Aken WG, Hirsh J *et al.* Impedance plethysmography using the occlusive cuff technique in the diagnosis of venous thrombosis. *Circulation* 1976; **53**: 696–700.
11. Comerota AJ, Katz ML, Grossi RJ *et al.* The comparative value of noninvasive testing for diagnosis and surveillance of deep vein thrombosis. *J Vasc Surg* 1988; **7**: 40–9.
12. Cronan JJ, Dorfman GS, Grusmark J. Lower extremity deep venous thrombosis: further experience and refinements of US assessment. *Radiology* 1988; **168**: 101–7.
13. Vogel P, Laing FC, Jeffrey RB, Wing VW. Deep venous thrombosis of the lower extremity: US evaluation. *Radiology* 1987; **163**: 747–51.
14. Raghavendra BN, Harii SC, Hilton S, Subramanyam BR, Rosen RJ, Lam S. Deep venous thrombosis: detection by probe compression of veins. *J Ultrasound Med* 1986; **5**: 89–95.
15. Dauzat MM, Laroche JP, Charras C *et al.* Real time B mode ultrasound for better specificity in the noninvasive diagnosis of deep venous thrombosis. *J Ultrasound Med* 1986; **5**: 625–31.
16. Comerota AJ, Katz ML, Greenwald LL, Leefmans E, Czeredarczuk M, White JV. Venous duplex imaging: should it replace hemodynamic tests for deep venous thrombosis? *J Vasc Surg* 1990; **11**: 53–61.
17. Borozan PG, Zukowski A, Thorpe L, Auer AI, Caracci BF. Noninvasive imaging for deep venous thrombosis. *Am J Surg* 1988; **156**: 474–6.
18. Lensing AW, Prandoni P, Brandjes D *et al.* Detection of deep vein thrombosis by real-time B-mode ultrasonography. *N Engl J Med* 1989; **320**: 342–5.
19. Kakkar VV, Lawrence D. Hemodynamic and clinical assessment after therapy for acute deep vein thrombosis: a prospective study. *Am J Surg* 1985; **150**(4A): 54–63.

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Limitations of ultrasonography in surveillance of small abdominal aortic aneurysms

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The repeatability, observer bias and instrument bias of aortic diameter measurement by ultrasonography, were investigated in ten patients with small (3–6 cm by computed tomography) infrarenal abdominal aortic aneurysm. The repeatability of maximum aortic diameter measurement by ultrasonography was much better for anterior–posterior than transverse diameter, with coefficients of repeatability 3·0–7·5 mm and 10–15 mm respectively. The repeatability of suprarenal aortic diameter measurement was poor. Surprisingly, maximum diameter using ultrasonography was larger than that using computed tomography, the difference being least for anterior–posterior measurements. At best a single, experienced observer, using the same instrument may provide aortic diameters using ultrasonography accurate to within 5 mm, but more commonly such aortic diameter is only accurate to within 8 mm.

Screening for abdominal aortic aneurysm with ultrasonography has become popular and has been advocated as a cost-effective procedure[1–3]. Ultrasound screening of selected populations identifies many small aneurysms of maximum diameter <5 cm. The benefits of surgery in such patients is unproven and one option is to monitor carefully the aorta for increasing dilatation. A randomized, multicentre trial of early surgery or observation for small asymptomatic abdominal aortic aneurysm would be an appropriate method of establishing the better patient management. While ultrasonography is a reliable screening method for identifying dilatation of the infrarenal aorta, the reliability of ultrasound in providing comparable diameters with different instruments in separate centres or information about the growth rate of small aneurysms has not been established. In this study we describe the variability of measurement by ultrasound in ten patients with maximum infrarenal aortic diameters of 3–6 cm. The results are compared with those of computed tomography (CT) and clinical assessment.

Patients and methods

Ten patients, with clinical evidence of infrarenal aortic dilatation, attending the Charing Cross Arterial Clinic were invited to participate in the study. The maximum external aortic diameter of all ten was assessed clinically and by ultrasonography on two separate occasions 3 weeks apart, and by CT scan once. No growth of small aneurysms would be expected during the 3-week interval. The clinical assessment of maximum aortic diameter was performed by a consultant vascular surgeon and three of his trainee surgeons. Ultrasound estimations included maximum external infrarenal transverse and anterior–posterior diameter and suprarenal transverse and anterior–posterior diameter. The ultrasound determinations were made first by two observers, an experienced vascular technician (A) using an Acuson 128 Colour Duplex (Acuson, Stevenage, UK) with 3·5 MHz probe (linear array) and an ultrasonographer (B) using a Siemens Sonoline 2 (Siemens, Sunbury-on-Thames, UK) with 3·5 MHz probe (mechanical sector). The ultrasound determinations were then repeated after the observers had exchanged instruments. The patients were then transfered from Charing Cross Hospital to another London teaching hospital, where an ultrasonographer (C) using an Acuson 128 Duplex with 3·5 MHz probe (linear array) made a repeat ultrasound examination. Calipers were placed by the observer at the maximum diameter and the size recorded by a separate person. Observers were blind to all measurements. The diameter was measured three times on both visits, giving six estimates of each diameter in a particular patient from each of five observer–instrument combinations. The repeatability of diameter measurement by ultrasonography was estimated[4] and observer–instrument variations analysed by the method of Bland and Altman[5]. We also compared maximum external diameter from ultrasonography and CT scan for the ten patients and the different observer–instrument combinations using the paired t test. Similarly, the maximum transverse infrarenal diameter measured manually was compared with maximum external diameter determined by CT scan and ultrasonography. An additional nine patients suspected of having a small abdominal aortic aneurysm were included for the comparison of manually and ultrasonographically measured transverse diameter.

Results

Clinicians could always detect and diagnose an aortic aneurysm when the maximum diameter by CT scan was >4 cm, but their estimate of aneurysm size was inaccurate. There was no correlation between the maximum transverse infrarenal aortic diameter as measured by CT scan or ultrasonography and the manual diameter measured by an experienced clinician (*Figure 1*). The mean difference between manually and ultrasonographically measured diameter was 3·2 mm (95 per cent confidence limit −2·9 to +9·2) but the standard deviation (s.d.) of the differences was 30 mm, indicating wide limits of agreement[5]. Limited information about aneurysm size can be obtained from clinical assessment.

The repeatability of ultrasound measurement can be assessed from the repeated measurements at each visit by the same observer on the same instrument. The coefficient of repeatability indicates that 95 per cent of the results lie within this distance from the mean, provided the mean difference is not significantly different from zero[4]. For maximum infrarenal diameter using ultrasonography the coefficient of repeatability for anterior–posterior and transverse diameter was 3·0–7·5 mm and 10·2–15·4 mm respectively. The coefficient of repeatability did not improve when the smaller diameter aortas were excluded. For suprarenal diameter the coefficient of repeatability was best for anterior–posterior diameter, 10–14 mm. This superiority of anterior–posterior diameter over transverse diameter measurement received further support from the comparison of diameter measured by ultrasound and by CT scan.

The maximum aortic diameter determined by ultrasound was consistently larger than that by CT scan. While the mean differences for maximum anterior–posterior diameter were small, 0·1–3·1 mm, the mean differences for maximum transverse diameter were significantly larger, 3·2–9·1 mm,

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$0{\cdot}02 > P > 0{\cdot}001$ (mean difference 3·2, 95 per cent confidence interval 0·6 to 5·7 mm; mean difference 9·1, 95 per cent confidence interval 5·9 to 12·3 mm). A comparison of the diameter by CT scan with the corresponding diameter by ultrasonography (*Figure 2*) illustrates the apparent magnification by ultrasound, the variation of ultrasound measurement which did not decrease with increasing aortic diameter, and the superiority of the anterior–posterior measurement using ultrasonography. The anterior–posterior diameter by ultrasonography is used for all further comparisons.

Another measurement that has been proposed to increase the specificity of ultrasonographic diagnosis of aneurysm is the ratio of suprarenal to maximum infrarenal diameter. Although the suprarenal aorta was ultrasonographically imaged on all occasions, the diameter for any patient varied from 75 per cent to 165 per cent of the corresponding diameter by CT scan and the coefficient of repeatability was poor. Therefore, suprarenal diameters were not further evaluated.

Intraobserver variation was assessed by comparing the maximum anterior–posterior diameter by ultrasonography measured by the same observer using the same instrument at the two visits, between which growth should not have occurred. In the four observer–instrument combinations involving observers A and B, there was no significant difference in diameter, mean difference −0·1 to −1·0 mm with 95 per cent confidence intervals not exceeding ±4 mm. The fifth observer–instrument combination (observer C) reported a significant increase in maximum anterior–posterior aortic diameter at the second visit, mean difference 4·8 mm (95 per cent confidence interval 2·5 to 7·2 mm), $P < 0{\cdot}001$ (*Table 1*).

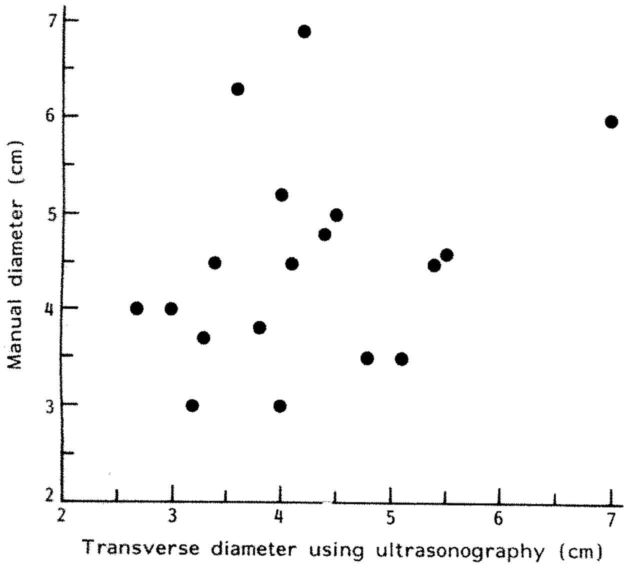

Figure 1 *Comparison of transverse diameter measurement of small abdominal aortic aneurysms manually and by ultrasonography. Diameter determined with the clinicians' hands and a ruler (manual) is shown on the vertical axis and the maximum external transverse infrarenal aortic diameter by ultrasonography is plotted on the horizontal axis. A correlation line can be drawn, r=0·3, but the relationship is not statistically significant*

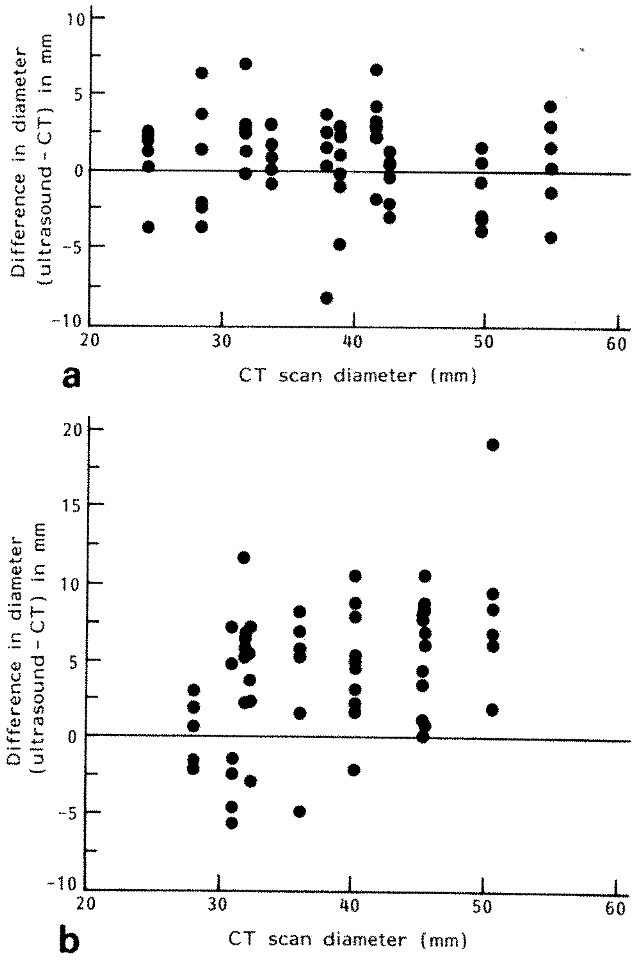

Figure 2 *Variation of maximum external aortic diameter by ultrasonography and its comparison with computed tomography (CT). (a) anterior–posterior diameter; (b) transverse diameter. Points show the mean diameters obtained by the three ultrasonographers using their most familar instrument at the two visits for each of the ten patients. The horizontal axis shows the corresponding diameters by CT scan*

Table 1 *Intraobserver and interobserver variation in measuring the maximum external anterior–posterior diameter of small abdominal aortic aneurysms by ultrasonography*

	Mean difference(s.d.) in mm									
	A_a1	B_a1	A_s1	B_s1	C_a1	A_a2	B_a2	A_s2	B_s2	C_a2
A_a1		−2·8(2·3)	−1·0(1·6)	−1·3(1·7)	−1·9(4·0)	−0·7(3·3)	−3·8(3·3)	−1·1(5·6)	2·1(3·3)	3·0(2·8)
B_a1			−1·8(2·0)	−1·5(2·7)	−4·7(3·7)	−2·0(3·6)	−1·0(2·8)	−1·7(5·6)	0·7(3·9)	
A_s1				−0·3(1·7)	−2·9(4·0)	−0·2(3·3)	2·8(3·2)	−0·1(5·2)	−1·1(3·5)	2·0(2·0)
B_s1					−3·2(4·5)	−0·6(3·5)	2·5(3·1)	−0·2(5·6)	−0·8(3·8)	1·7(2·4)
C_a1						−2·6(3·8)			−4·0(4·1)	−4·8(3·3)
A_a2							−3·0(2·5)	−0·3(4·1)	−1·3(2·3)	2·2(3·1)
B_a2								−2·7(4·2)	1·7(2·7)	−0·8(3·0)
A_s2									−1·0(3·7)	1·9(4·6)
B_s2										0·9(3·5)
C_a2										

A, B, C refer to three different observers; a, Acuson instrument; s, Siemens instrument; 1 and 2, separate visits

Differences in the relative magnitudes of diameter by ultrasound obtained with the different observer–instrument combinations might result from observer or instrument bias. This was investigated by comparing the measurements obtained from observers A and B each using two different ultrasound instruments. The choice of instrument did not influence significantly the maximum anterior–posterior diameter, although the most experienced observer (B) had a tendency to report larger diameters using the Acuson 128 Colour Duplex compared with using the Siemens Sonoline 2, with mean differences 0·7–2·5 mm (*Table 1*). The observer bias was important, with observer B measuring larger diameters than observer A on both ultrasound instruments, mean difference 0·3–3·0 mm, 95 per cent confidence interval −0·3 to 1·5 mm ($P<0{\cdot}5$) and 1·2 to 4·8 mm ($P<0{\cdot}005$) at the extreme mean differences.

Collaborative efforts are often necessary to provide sufficient patients for a particular study but standardization of and agreement between measurements may be a problem. The agreement between ultrasound measurements of maximum external aortic diameter was assessed with each of the three observers using the ultrasound equipment with which they were most familiar. The range of diameters is shown in *Figure 2*. The mean(s.d.) differences are shown in *Table 1* (columns A_a, B_s and C_a). The limits of agreement are calculated from mean (2 s.d.) difference[5]. The mean differences varied from −3·0 to +4·0 mm, with s.d. varying between 1·7 and 4·5 mm, giving a widest limit of agreement −5·8 to +12·2 mm (B_s1/C_a1). These results (*Table 1*) illustrate the problems and inaccuracies that arise in comparing diameters obtained by ultrasonography in different centres and suggest that only differences of >8 mm would be significant.

The data could also be analysed in another way. If the policy at a particular screening centre was to offer surgery to patients with a maximum aortic diameter of ⩾5 mm only one patient would have been offered an operation as the result of CT scan. This patient would also have had a 100 per cent chance of being offered an operation as the result of ultrasound screening (all measurements >5 cm). However, using ultrasonography, four further patients might have been offered an operation: two of these patients (transverse CT scan diameters 3·6 and 4 cm) would have had a 10 per cent chance of being offered an operation, two patients (CT scan diameters 4·5 cm) would have had a 40 per cent and 70 per cent chance respectively of being offered an operation. This situation is far from satisfactory.

Discussion

The clinician often detects an abdominal aortic aneurysm first by palpation of the transverse diameter, but his estimate of size is inaccurate. The diameter may be more accurately estimated by CT scan or ultrasonography. Ultrasonography offers a rapid, convenient, sensitive method of screening for abdominal aortic aneurysm. Moreover the planes achieved by ultrasonography should avoid overestimation of aortic diameter in a tortuous aorta, whereas the transverse plane in CT might scan an oval lumen in tortuous vessels with resultant overestimation of the maximum aortic diameter. Surprisingly, the present results demonstrate that the diameter by ultrasonogrphy of small aortic aneurysms is greater than the corresponding diameter estimated by CT scan. The results demonstrate that measurement of maximum aortic anterior–posterior diameter by ultrasonography is more repeatable and more concordant with the CT scan result than the corresponding transverse diameter measurement.

Several retrospective studies have attempted to deduce the growth rates of aneurysms[6,7]. The most recent of these commented on the difficulty of this task, 'There have been, to our knowledge, no published data regarding intraobserver or interobserver variation in the estimation of the size of aneurysms on ultrasound examination'[7]. Some screening programmes have reported that many aneurysms appear smaller on second ultrasound assessment. Where studies have used several different observers, only a difference in anterior–posterior diameter of >8 mm is likely to signify real growth. From the present study, we would expect a change in anterior–posterior diameter of >5 mm to signify growth if a single, experienced observer using the same ultrasound instrument made the measurement. Because the inaccuracy of ultrasonography appears to be independent of the magnitude of the anterior–posterior diameter of a small aneurysm (3–6 cm), the proportional error is most for small aneurysms.

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References

1. Collin J, Araujo L, Walton J, Lindsell D. Oxford screening programme for abdominal aortic aneurysm in men aged 65–74 years. *Lancet* 1988; **ii**: 613–15.
2. Scott RAP, Ashton HA, Kay DN. Routine ultrasound screening in management of abdominal aortic aneurysm. *Br Med J* 1988; **296**: 1709–10.
3. O'Kelly TJ, Heather BP. General practice-based population screening for abdominal aortic aneurysm: a pilot study. *Br J Surg* 1989; **76**: 479–80.
4. British Standards Institution. *Precision of Test Methods 1: Guide for the Determination and Reproducibility for a Standard Test Method* (BS 5497, part 1). London, BSI, 1979.
5. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **i**: 307–10.
6. Littooy FN, Steffan G, Greisler HP, White TL, Baker WH. Use of sequential B-mode ultrasonography to manage abdominal aortic aneurysms. *Arch Surg* 1989; **124**: 419–21.
7. Nevitt MP, Ballard DJ, Hallett JW. Prognosis of abdominal aortic aneurysms: a population based study. *New Engl J Med* 1989; **321**: 1009–14.

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Groin wound infection after arterial surgery

Fifty-six patients, 30 with superficial and 19 with deep groin wound infections, and seven with lymph fistulae with positive cultures within 30 days of arterial surgery, were identified after 661 operations (873 groins at risk) between September 1984 and August 1988. The commonest infecting organisms were Staphylococcus aureus, Pseudomonas aeruginosa *and* Proteus *spp. In 33 patients the infection settled completely after treatment with culture specific antibiotics. These were given intravenously then orally for up to 6 weeks. Sixteen patients required debridement and excision of necrotic wound edges, including one who had an antibiotic infusion into the wound. Graft excision was performed in seven patients of whom five received an extra anatomic bypass. The need for graft excision was much greater (six versus one) for Dacron® and/or polytetrafluoroethylene than for vein. In two lymph fistulae sartorius transposition and wound resuture were used. All groins healed, though three extremities were ischaemic following occlusion of the bypass. There were two deaths, one from myocardial infarction and one from pulmonary embolism and no major amputations. These results suggest that most infective groin problems may be successfully managed conservatively and that radical graft excision is only necessary for a few intractable cases.*

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Groin wound infection and lymph fistulae are troublesome complications of reconstructive surgery involving the femoral arteries[1–6]. Most problems are superficial, causing no more than local discomfort and prolongation of hospital stay. However, deep infections can spread to threaten a suture line. Radical excision and extra anatomic bypass have a high (25–75 per cent) mortality and 35–75 per cent limb loss[2,4–6].

In consequence, alternative less radical approaches have been developed for deep infections which have been complicated by haemorrhage, and this retrospective review was undertaken to see if a selective trend towards more conservative surgical procedures is justified.

Patients and methods

Fifty-six (6·4 per cent) superficial or deep groin wound infections and lymph fistulae with positive cultures within 30 days of arterial surgery were identified among 873 groins at risk. These occurred after Dacron® (E.I. de Pont de Nemours and Company, UK) to femoral artery anastomosis for proximal reconstruction, femoral embolectomy, profundaplasty and proximal anastomosis for 173 femorodistal bypasses (*Table 1*). Superficial wound infection was defined as wound erythema with a serosanguinous discharge; deep infection was characterized by the presence of frank pus, necrotic wound edges and deep extension[7]. Lymph fistula is a separate entity with a watery discharge which started a few days after operation and usually became secondarily infected. The data on wound infections was recorded prospectively in a computerized vascular audit of 661 consecutive primary arterial operations performed between September 1984 and August 1988. Cases not involving exposure of the femoral arteries were excluded.

In the 56 infected cases, the original indications for surgery had been: critical ischaemia (28), intermittent claudication (17), acute embolus (6) and false aneurysm (5). The operations after which infection occurred are shown in *Table 2*. The implant material was Dacron or polytetrafluoroethylene (PTFE) in 24 and autogenous vein in 22. No bypass was inserted in ten (six embolectomies, three profundaplasties and one operation for false aneurysm).

Patients routinely received antibiotic prophylaxis using an intravenous broad spectrum cephalosporin, commencing at induction of anaesthesia with two further doses after operation. Early in the series flucloxacillin was used in some cases. Topical antibacterials were not used before operation or during wound closure. Meticulous attention was paid to haemostasis and elimination of dead spaces.

Results

There were 30 superficial and 19 deep wound infections and seven lymph fistulae. The onset was at a mean of 7 days after operation (range 3–12 days). The male:female ratio was 2:1

Table 1 *Graft materials for femorodistal bypass*

Graft material	No.
In-situ vein	133
Reversed vein	17
PTFE	14
Vein/PTFE composite	7
Umbilical vein	1
Dacron	1
Total	173

PTFE, polytetrafluorethylene

Table 2 *Operations complicated by groin wound infection*

Operation	Infected	Total	Percentage infected
Femorodistal and iliopopliteal (4) bypass	24	177	13·5
Aortobifemoral bypass	9	131	6·9
Iliofemoral bypass	6	53	11
Femoral embolectomy	6	145	4·1
Femoral anastomotic aneurysm repair	5	35	14
Femorofemoral bypass	3	81	4
Profundaplasty	3	39	8
Total	56	661	8·5

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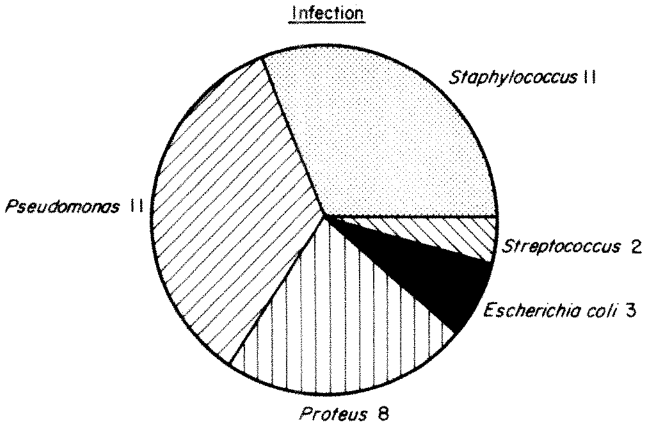

Figure 1 *Single organisms identified in 35 infections*

Table 3 *Risk factors for wound infection after arterial surgery in the groin*

Distant infective source	19
Previous groin surgery	11
Early re-exploration	
Haemorrhage	7
Thrombosis	11
Jejunal leak	1

and the median age was 70 years. There were two postoperative deaths, neither related to a graft complication (myocardial infarction and pulmonary embolus respectively). There were three graft occlusions (two after femoropopliteal bypass and one after femorofemoral bypass). The mean hospital stay after operation for infected cases was 29 days, compared with 12 day for non-infected cases. There were no amputations.

Infective organisms were identified in all cases (*Figure 1*). A single organism was cultured in 35 of which *Staphylococcus aureus* and *Pseudomonas aeruginosa* were commonest. From 21 infections there were mixed cultures including anaerobic *Bacteroides* species. Risk factors associated with the development of wound infection are shown in *Table 3*. Most infections were superficial and were associated with poor healing after a long thigh incision for femorodistal bypass. This incidence was reduced by more accurate preoperative mapping of the long saphenous vein using duplex ultrasonography.

Treatment is outlined in *Figure 2*. All patients received culture specific antibiotics, intravenously and then orally for at least 5 days for minor infections, and for up to 6 weeks for more serious infections. Two or more drugs were used in 40 patients. Thirty patients had superficial infection and in 22 the wounds healed with antibiotics, bed rest and local dressings; eight wounds required excision or secondary suture.

There were 19 deep infections. Six healed with antibiotics alone. Their vascular components included three femoropopliteal vein bypasses, a femoral embolectomy and two limbs of Dacron bypasses (one aortofemoral and one femorofemoral). A further six required debridement and excision of necrotic wound edges including one with an antibiotic irrigation to clean the wound and encourage granulation. Four aortobifemoral bypasses were completely removed with oversewing of the aortic stump, followed in two by an axillobifemoral bypass. In the remaining three deep prosthetic infections, removal of Dacron was confined to the affected groin since the remainder of the prosthesis was well incorporated and was clinically uninvolved. In three cases, the leg was revascularized by femorofemoral bypass, obturator bypass and subscrotal bypass[8,9] (*Figure 3*).

There were seven lymph fistulae. Five settled with antibiotic therapy alone. The other two resolved after sartorius transposition and re-suture of the wound.

Similar numbers of infected groin wounds contained autogenous vein (22) and Dacron or PTFE (24). The need for graft excision was much greater (six versus one) for Dacron or PTFE than for vein (*Figure 4*). Even so, the great majority of non-haemorrhagic infections settled without recourse to radical excision irrespective of the underlying implant material.

Discussion

Postoperative groin wound infections stem largely from the patients' own organisms. Resident skin flora are particularly common causes but two other routes of entry exist. In advanced foot ischaemia, bacteria adjacent to trophic lesions appear in the groin lymph nodes by lymphangitis-like spread[2]. Consequently, the operative wound can become contaminated when inguinal lymphatics are transected while gaining access to the femoral artery.

Secondly, the groin is particularly vulnerable to colonization by perineal organisms related to the anogenital orifices. In our study, *Pseudomonas* and *Proteus* species were common, supporting the role of these factors in causation. Efforts to sterilize the groin area before operation are ineffective[10] and some have even tried to avoid the groins completely by performing distal anastomoses to the external iliac arteries through an abdominal incision.

Most wound infections are superficial. However, early complications are worrying as they may presage a deep infection with the risks of chronic wound sinus, anastomotic disruption causing secondary haemorrhage, septicaemia and graft thrombosis. Further, the incidence of late anastomotic false aneurysm is increased if the initial bypass is complicated by a superficial wound infection[11].

Fortunately, most superficial wound infections are effectively treated with antibiotics and local dressings, though the hospital stay is extended to twice the normal duration. Most lymph fistulae resolve within a few days. However if the discharge is copious and persistent a sartorius muscle transposition[6], inferior rectus abdominis or omental flap[2] may be considered.

The management of deep infection is more controversial with conflicting advice, some advocating radical excision and others championing a more cautious approach[4–6,12]. Our experience leads us to the conclusion that a single radical approach to all deep groin infections is an over reaction. Each case should be considered individually. We have been encouraged by our initial results; haemorrhage has not occurred with techniques such as heterotopic local bypass[13,14] and wound irrigation, though more experience is needed before firm guidelines are established.

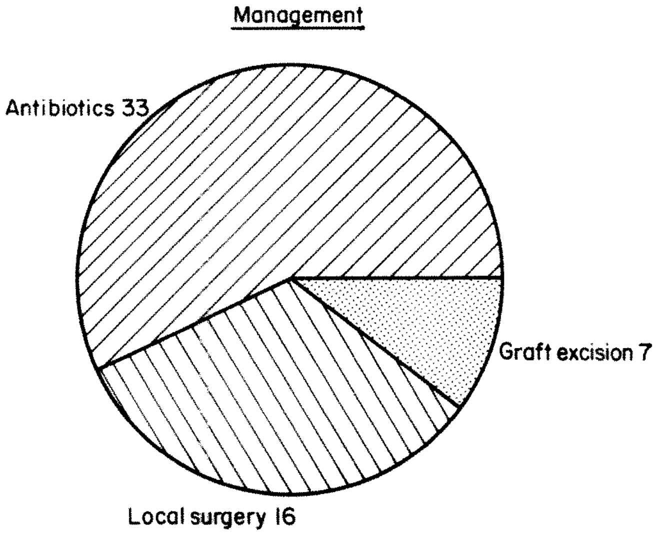

Figure 2 *Management of groin wound infections and lymph fistulae*

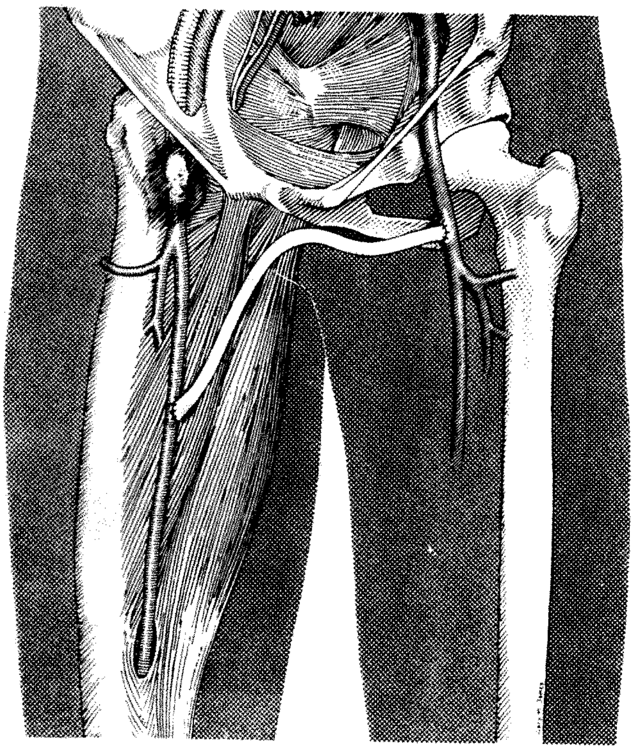

Figure 3 *Subscrotal bypass from the contralateral femoral artery. Also known as transperineal bypass*[9] *and* pontage perineux[8]

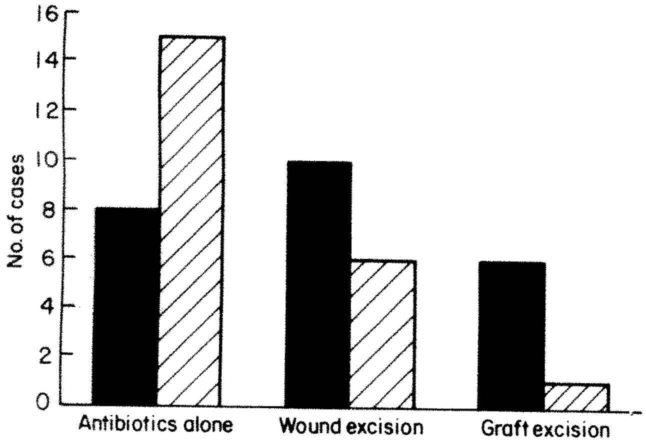

Figure 4 *Comparison of treatment according to the underlying implant material.* ■, *Dacron/polytetrafluoroethylene;* ▨, *vein*

No amputations were required in the present series, and there was no uncontrolled sepsis or crosscontamination of a remote bypass. Experience with orthotopic bypass of mycotic aneurysms[15] supports a trend towards surgical conservatism. Inevitably, there will be some patients for whom a radical excision cannot be avoided, at the increased risk of death and limb loss, but the present results illustrate that this should be necessary only in a few intractable cases.

Acknowledgement

We would like to thank Gary M. James for the illustrations.

References

1. Bennian RS, Williams RA, Wilson SE. Surgical management of uni-lateral groin infection after aorto-femoral bypass. *Surg Gynecol Obstet* 1983; **156**: 724–8.
2. Kretschmer G, Niederle B, Huk J *et al.* Groin infection following vascular surgery; obturator bypass versus biological coverage. *Eur J Vasc Surg* 1989; **3**: 25–9.
3. Popovsky J, Singer S. Infected prosthetic graft; local therapy with graft preservation. *Arch Surg* 1980; **115**: 203–5.
4. Kwaan JHM, Connolly JE. Successful treatment of prosthetic graft infection with continuous povidone–iodine irrigation. *Arch Surg* 1981; **116**: 716–20.
5. Almgren B, Erikson I. Local treatment of infected arterial grafts. *Acta Chir Scand* 1985; **529**: 91–4.
6. Laustsen J,Bille S, Christensen J. Transposition of sartorius muscle in the treatment of infected vascular grafts in the groin. *Eur J Vasc Surg* 1988; **2**: 111–13.
7. Szilagyi DE, Smith RF, Elliot JP *et al.* Infection in arterial reconstruction with synthetic grafts. *Ann Surg* 1972; **176**: 321–33.
8. Kieffer E *et al.* Pontage perineux fémoro-fémoral par le périnée (6 observations). *Chirurgie* 1976; **102**: 420–8.
9. Taylor RS, Massouth F. The transperineal graft – an alternative route for femoro-femoral bypass. In: Greenhalgh RM, ed. *Extra-anatomic and Secondary Arterial Reconstruction.* London: Pitman, 1982: 237–43.
10. Earnshaw JJ. Do preoperative chlorhexidine baths reduce the risk of infection after vascular surgery. *Eur J Vasc Surg* 1989; **3**: 322–6.
11. Clarke AM, Poskitt KR, Baird RN, Horrocks M. Anastomotic aneurysms of the femoral artery: aetiology and treatment. *Br J Surg* 1989; **76**: 1014–16.
12. Ghosh P, Rabbat A, Trudel J. Why remove an infected aorto-femoral graft? *Can J Surg* 1983; **26**: 330–31.
13. Geroulakos G, Parvin SD, Bell PRF. Obturator foramen bypass, the alternative route for sepsis in the femoral triangle. *Acta Chir Scand* 1988; **154**: 111–12.
14. Shaw RS, Bauer AF. Management of sepsis complicating arterial reconstructive surgery. *Surgery* 1969; **53**: 57–86.
15. Baird RN. Mycotic aortic aneurysms. *Eur J Vasc Surg* 1989; **3**: 95–6.

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Clinical outcome and health care costs in renal revascularization – percutaneous transluminal renal angioplasty versus reconstructive surgery

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Clinical outcome and health care costs related to investigation, treatment with either percutaneous transluminal renal angioplasty (PTRA) or reconstructive surgery, and follow-up of patients with renovascular hypertension with or without uraemia were analysed in 21 PTRA-treated and 16 operated patients. Most renal artery stenoses were atherosclerotic. Nineteen PTRAs were successful or partly successful and two failed; the patients were operated on without delay. All surgical reconstructions were successful. In the PTRA group six restenoses occurred after 4–24 months. Four were treated with re-PTRA and two were operated on. No recurrence occurred in the operated group. At the end of follow-up (median 48, range 9–84 months) primary patency in the PTRA group was 69 per cent and in the operated group 100 per cent. Secondary patency in the PTRA group was 100 per cent. With regard to hypertension, including primary and secondary results, 19 out of 21 (90 per cent) patients were improved in the PTRA group and 13 out of 16 (81 per cent) in the operated group. The diagnostic and preprocedure costs were the same in both groups, whereas the procedure and postprocedure costs were lower in the PTRA group. However, the follow-up costs were considerably higher because of recurrences and their treatment in the PTRA group. The total median cost of reconstructive surgery was 12 per cent higher than for PTRA, a non-significant difference.

The development of a double lumen polyvinyl balloon catheter by Grüntzig *et al.* introduced a new treatment option in renovascular occlusive disease[1]. Percutaneous transluminal renal angioplasty (PTRA) is a minor procedure compared with reconstructive renovascular surgery and hospital stay is shorter. However, if judged by the same criteria as operation, PTRA has a complication rate much higher than was first thought[2,3]. Moreover, the recurrence rate seems to be higher after PTRA than after reconstructive surgery, necessitating repeated dilatation or surgery[4–6]. Nevertheless, a retrospective analysis presented in 1987 by England *et al.*[7] concluded that PTRA was more cost-effective than surgery in elderly atherosclerotic patients.

The aim of this study was to analyse the clinical outcome and health care costs of PTRA and operation, including diagnostic investigation, preprocedure assessment, procedure and post-procedure care, complications and recurrences, the treatment of these, and the long term follow-up. All outcomes and costs were referred to the initially chosen procedure and the patients were thus divided into two groups, the PTRA group and the operated group.

Patients and methods

From January 1981 to December 1982, 21 patients were treated with PTRA (PTRA group) and 16 with reconstructive renovascular surgery (operated group) at Malmö General Hospital. The indication was renovascular hypertension with or without impending uraemia. All patients had severe hypertension with inadequate pharmacological control. The time period chosen excluded the initial learning period for PTRA (1979–1980). The inclusion period of 2 years was chosen to give at least a 4-year follow-up period. For both groups the median follow-up time was 48 months (range 9–84 months). Clinical characteristics did not significantly differ between the two groups (*Table 1*).

All patients were considered candidates for treatment with either PTRA or surgery. The decision whether to treat with PTRA or surgery

Table 1 *Characteristics of patients*

	PTRA group	Operated group	Significance
No. of patients	21	16	
Male/female ratio	10/11	10/6	
Median age (range)	61 (31–76)	51 (18–83)	n.s.
Diagnosis			
atherosclerosis* (%)	18 (86)	14 (87)	n.s.
fibromuscular dysplasia	3	2	n.s.
Median serum creatinine in μmol/l (range)	131 (85–409)	116 (79–407)	n.s.
No. of patients with serum creatinine >150 μmol/l (%)	9 (43)	6 (37)	n.s.
Median duration of hypertension in months (range)	50 (5–360)	35 (2–252)	n.s.
Mean number of antihypertensive drugs	3·5	3·7	n.s.

PTRA, percutaneous transluminal renal angioplasty; *lesions within 1 cm from the contrast column in aorta, shorter than 1 cm and tapering, i.e. isthmus and juxta-aortic stenoses

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was made after informing the patients of the advantages and disadvantages of each type of treatment. The choice of the patient was respected and if the patient had no preference the earliest available method was chosen. Thus, the two samples were not randomized.

Diagnostic evaluation and preprocedure preparation

Diagnostic evaluation was made in hospital. The routine preparation included standard laboratory tests (haemoglobin, sedimentation rate, serum sodium, serum potassium, serum creatinine), peripheral renin estimation, creatinine clearance estimation, electrocardiogram, chest radiograph, selective renal vein catheterization for renin determination, and renal angiography. If there was a delay between diagnostic evaluation and the availability of treatment, the standard laboratory tests, electrocardiogram and chest radiograph were repeated. The operability of each patient was thus evaluated and pharmacological treatment was optimized. The possibility of dilatation was judged at angiography by an experienced radiologist. The indication for revascularization was unresponsive hypertension in the presence of significant renal artery stenosis. The criteria of significance were based on angiography, pressure gradient and selective renal vein renin studies. Stenosis in the main renal artery was considered significant in the presence of any one of the following: renal artery diameter 2 mm or less, pressure gradient >20 mmHg, ratio of stenotic:non-stenotic renal vein renin concentration $\geqslant 1{\cdot}5$[8]. Poststenotic dilatation, obvious collateral circulation and decreased kidney size were regarded as less important[8]. A stenosis was considered atherosclerotic if shorter than 1 cm in length and located within the first centimetre from the contrast agent column in the aorta. 'Istmus' and 'juxta-aortic' stenosis was included. String of beads sign, membranous and distally located stenosis were considered to indicate fibromuscular dysplasia.

Procedure

The night before PTRA patients were hydrated with intravenous infusion of 1000 ml Ringer-glucose which was repeated during the PTRA procedure. Prophylactic antibiotics (intravenous dicloxacillin 2 g) were given 1 h before PTRA since 1982. During the procedure, patients were given intra-arterial heparin (30 units per kg body-weight) and 4 h later 500 ml intravenous dextran 40 was given over 4–6 h. Dilatation was performed manually by inflating the balloon with diluted contrast medium. The stenoses were dilated for 15–20 s three or four times or until the balloon was no longer deformed by the stenosis. Aortography was then performed to check the results.

In the operated group prophylactic antibiotic was given at the time of anaesthesia induction and 500 ml dextran 40 was given during surgery. Another 500 ml was given during the first 12 h after operation. Surgery was performed transperitoneally through a transverse abdominal incision. In atherosclerotic patients thromboendarterectomy (TEA) and patch graft was performed as reconstruction. In the two patients with fibromuscular dysplasia arteriotomy and patch graft was performed.

Post-procedure

Care after the procedure included standard laboratory tests, creatinine clearance estimation and renal angiography. After operation the patient was routinely observed in the intensive care unit for 1 day, or longer if necessary, and thereafter in the ordinary ward. Patients in the PTRA group were observed in the ordinary ward with regard to renal function and blood pressure. Dextran 40 (500 ml) was given intravenously on days 1, 2 and 3 after the procedure.

Follow-up

Patients were scheduled for follow-up evaluation 1, 3, 6, 9, 12, 18, 24, 36, and 48 months after the procedure. Complications and recurrences were scrutinized and registered in a similar way for both groups in the short term, i.e. within the first 30 days of the procedure, and in the long term, i.e. until end of follow-up. When evaluating clinical results at the end of follow-up with regard to hypertension, patients were considered cured if the diastolic blood pressure was $\leqslant 90$ mmHg without antihypertensive medication. Improved were those who had: (1) reduction in diastolic pressure of 15 mmHg or more without medication, (2) diastolic pressure of $\leqslant 90$ mmHg with unchanged antihypertensive medication but diastolic pressure reduction of 15 mmHg or more, (3) diastolic blood pressure of $\leqslant 90$, on less medication than required before treatment. Failures were those who did not qualify for either of the above categories.

Long term technical results were judged by clinical signs in the absence of hypertension or in case of hypertension by reangiography. Patency was defined as absence of significant renal artery stenosis, primary if it was achieved after the initial procedure, or secondary if one or more additional procedures had to be performed. In patients who died during follow-up renal arteries were examined at autopsy; the results up until the time of death were recorded.

If recurrence occurred it was first treated with re-PTRA if the radiologist judged the stenosis possible to dilate; otherwise surgery was chosen. Furthermore, in cases of markedly reduced renal function (serum creatinine $\geqslant 300$ mmol/l) surgery was preferred because of the risk of contrast medium toxicity in this patient category.

Costs of revascularization

Retrospective calculation of the total health care costs, based on data available for the 37 patients, was performed for each procedure. Estimation included case-specific costs as well as general hospitalization costs. Case-specific costs, i.e. actual resources used as specified in patient records included laboratory and diagnostic tests, revascularization procedures, physician visits etc., whereas general hospitalization costs included board and lodging. Altogether, these costs represent the direct costs (i.e. health care resource use) of renal revascularization. Indirect costs, i.e. productivity losses due to temporary illness, permanent disability or premature death were not included in the calculation[9].

Statistics

The Mann–Whitney test and *t* test were used to determine the significance of differences in contingency tables. Fisher's exact test was applied for analysis of factors in two-by-two tables.

Results

Technical results

In the PTRA group 17 of the 21 attempts at dilatation were successful, two were partly successful and two were impossible to perform. These last two patients, in whom stenoses of atherosclerotic origin could not be dilated, were successfully revascularized operatively with TEA and patch. In the operated group all 16 revascularizations were primarily successful.

Complications within 30 days (Table 2)

In the PTRA group the following major complications occurred: one patient had an occlusion of the iliac artery due to a guide wire lesion and was operated on (aortofemoral bypass), one patient had septic symptoms and one had pneumonia (both were treated with antibiotics). Three patients had minor complications, two of these had reversible renal insufficiency and one had a major groin haematoma.

In the operated group one patient developed retroperitoneal bleeding requiring several units of blood. Three patients were treated with antibiotics because of prolonged postoperative fever. One patient suffered from a postoperative pancreatitis complicated by abscesses requiring laparotomy and drainage. One patient had respiratory insufficiency, one myocardial infarction and cardiac decompensation needing a prolonged stay in the intensive care unit. Finally, four patients had renal insufficiency, reversible without dialysis.

Recurrences during follow-up (Table 2)

In the PTRA group six patients suffered from recurrent stenosis. All had deteriorated blood pressure control and were diagnosed by reangiography. In five patients the stenoses were atherosclerotic and were diagnosed at a median of 9 months (range 4–24 months) after the primary PTRA. In one patient with a fibromuscular dysplasia stenosis recurrence occurred 9 months after PTRA. In five of the recurrences the primary technical results were successful, and in one partly successful. Four of these patients were treated with re-PTRA. In one patient re-PTRA was unsuccessful making surgical treatment necessary. The final patient was treated with TEA and patch as the first revisional procedure. Recurrences occurred in both sexes and all age groups. In the operated group, no short or long term recurrence was noted. However, three patients were re-evaluated with angiography because of continuing hypertension. All had patent reconstructions.

Mortality

At the end of follow-up, 19 out of 21 PTRA patients and 14 out of 16 operated patients were alive. Four late deaths occurred, two in each group, 9–27 months after the initial procedure. The cause of death was cardiac failure in two patients, massive pulmonary embolism in one patient and a combination of progression of a contralateral renal tumour and cardiac failure in one.

Table 2 *Complications, recurrent stenosis and treatment*

	PTRA group	Therapy
Major early complications		
Attempted or failed PTRA	2	TEA + patch TEA + renal resection
Occlusion of the common iliac artery	1	Aortofemoral bypass
Septic symptoms	1	Antibiotics
Pneumonia	1	Antibiotics
Minor early complications		
Reversible renal insufficiency	2	1) Angiography 2) Computed tomography
Groin haematoma	1	Operation
Recurrent renal artery stenoses during follow-up	4	rePTRA
Recurrent renal artery stenoses during follow-up	1	a) rePTRA b) TEA + patch
Recurrent renal artery stenoses during follow-up	1	TEA + patch

	Operated group	Therapy
Retroperitoneal bleeding	1	Blood transfusion
Prolonged postoperative fever	3	Antibiotics
Pancreatitis	1	Laparotomy
Respiratory insufficiency	1	Intensive care unit
Myocardial infarction	1	Intensive care unit
Cardiac decompensation	1	Intensive care unit

PTRA, Percutaneous transluminal renal angioplasty; TEA, thromboendarterectomy

Results with regard to patency and blood pressure response

At the end of the follow-up, primary patency was 62 per cent (13 out of 21) in the PTRA group and 100 per cent in the operated group ($P = 0{\cdot}010$). Including secondary patency, 100 per cent was achieved also in the PTRA group (*Table 3*).

Primary results with regard to blood pressure showed 11 patients cured or improved and 10 failed in the PTRA group. Including secondary results in the PTRA group, 19 of the patients were improved and two failed with regard to blood pressure. In the operated group 13 patients were cured or improved and three failed with regard to blood pressure. Five out of six recurrent renal artery stenoses had atherosclerosis as the cause and four out of five non-responders with regard to blood pressure had stenoses of atherosclerotic origin.

Results with regard to costs

Table 4 illustrates health care costs per patient undergoing either surgical or angioplastic revascularization (for the sake of simplicity, diagnostic evaluation and preprocedure preparation have been added together). The preprocedure costs were similar in the two groups, whereas procedure costs differed markedly as did postprocedure costs. These differences are in favour of PTRA and reflect the less resource-demanding nature of this revascularization procedure and shorter hospital stay (median post-procedure hospital stay was 7 days in the PTRA group and 11·5 days in the operated group). The follow-up costs, however, were considerably higher in the PTRA group due to the additional diagnostic evaluation, additional pre and postprocedure costs and additional revascularization procedures. The additional hospital stay was a median of 22 days compared with 0 days in the operated group. As regards the total health care cost per patient, the median cost of surgery was 12 per cent higher than the median cost of the PTRA group. This difference was, however, not statistically significant.

Discussion

When introducing new technology it is important that proper comparisons are made with other therapeutic modalities as regards, for instance, technical short and long term results and complications. PTRA and reconstructive renovascular surgery are examples of different technologies with the same therapeutic goal, and we have previously suggested a standardized way to

Table 3 *Results on blood presure at the end of follow-up*

	PTRA group ($n = 21$)				Operated group ($n = 16$)			
	Primary	Secondary	Final		Primary	Secondary	Final	
Cured	2	–	2	(90)	4	–	4	(81)
Improved	9	8	17		9	–	9	
Failed	10		2	(10)	3	–	3	(19)

Primary results, after the primary treatment; secondary results, after nine revisional procedures in eight patients (two technical failures, six recurrent renal artery stenosis); final results, all procedures; values in parentheses are percentages

Table 4 *Health care costs in SEK* per patient in 1988*

	PTRA group		Operated group	
Period	Median	Range	Median	Range
Diagnostic evaluation and preprocedure preparation	23 900	9 900– 44 500	23 400	3 500– 43 200
Procedure	4 600	4 600– 37 200	26 000	20 600– 80 700
Postprocedure	10 400	3 100– 30 200	17 200	6 200– 63 000
Follow-up	26 200	2 000–166 000	6 100	1 600– 64 000
Total	65 100	30 700–250 800	72 700	42 100–227 000

*SEK, Swedish Crowns (SEK 100 = US$15)

analyse results and complications of these two therapeutic options[3]. However, economic analyses should also be performed in accordance with certain basic principles as regards identification, measurement and evaluation of consequences of the chosen alternatives[9]. The ability of non-economists to critically assess results from different economic analyses would clearly be improved if analyses were designed and performed in a standard manner[10,11]. The aim of this paper was to present clinical outcomes and health care costs for a consecutive patient series referred to Malmö General Hospital. The PTRA and the operated groups were similar with regard to age, gender, renal function and hypertensive history. The aetiology of stenosis was typical with about 80 per cent atherosclerosis and 20 per cent fibromuscular dysplasia[12,13].

The preoperative preparation was performed according to our standard protocol, regardless of whether PTRA or reconstructive surgery was chosen. At the time of recruitment in this study, about 300 surgical reconstructions had been performed at this hospital, but only 20 PTRAs. However, the initial learning period for PTRA was excluded.

Primary technical results after PTRA showed two failures out of 21 (10 per cent) and is similar to other reports. Ten major series have reported primary technical success of 56–100 per cent, most of them 80–90 per cent[14–23]. All these series had about the same proportion of fibromuscular dysplasia and atherosclerosis as in the present series. Atherosclerotic aetiology of renal artery stenosis is generally regarded as less favourable for treatment with PTRA, especially when the stenosis is localized close to the aorta[14,22,24]. The present results when only atherosclerotic stenosis is considered do not confirm this. There were about 12 per cent primary technical failures whch also was found by Geyskes[23]. Subdividing stenosis into ostial and juxta-aortic stenosis within the first centimetre from the aorta seems artificial because of our equally good therapeutic results. Fibromuscular dysplasia generally seems to allow a higher success rate, but a comparison with the present series is not worthwhile because of the small number of patients[23,25].

Long-term patency is inferior after PTRA compared with after surgery. A recurrence rate of 10–90 per cent is reported in the literature[4–6,25–31]. In the present series six out of 19 PTRAs (32 per cent) led to recurrence. Four of these were easily treated with rePTRA and two were surgically reconstructed. At the end of follow-up, secondary patency was 100 per cent. With regard to aetiology, five of 16 (31 per cent) recurrences occurred in patients with atherosclerosis and one of three in patients with fibromuscular dysplasia. One of two partly successful PTRAs led to recurrence which was easily treated with rePTRA. The other was patent at the end of follow-up.

The results after reconstructive renovascular surgery were 100 per cent both with regard to initial technical success and long term patency. This is in keeping with other studies. Technical success after surgery is reported in around 95–97 per cent[32–35], as is long term patency[35–37].

Complications within 30 days of operation occurred in 50 per cent of patients, causing prolongation of hospital stay and convalescence and, in one patient, a laparotomy because of pancreatitis. This complication is extremely rare and was the cause of the highest individual cost in the operated group – 227 000 SEK[38], although the median cost was only marginally affected.

In the PTRA group two procedures failed and one iliac artery occluded during the procedure. The renal arteries were reconstructed successfully as was the iliac artery through a bypass procedure. Nevertheless, it should be remembered that PTRA is not risk-free and this type of treatment should always be jointly managed by a team of physicians, radiologists and surgeons[2,3]. The surgeon must be familiar with vascular surgery and have a special interest in renovascular surgery.

Results with regard to blood pressure control

With regard to blood pressure control after surgery in mixed series with both atherosclerotic and non-atherosclerotic stenoses, cure or improvement is reported in 65–90 per cent and failures in 10–35 per cent, including primary and secondary results[20,39,40]. The present results are consistent with these reports. Primary results after PTRA are less favourable, with a 45–65 per cent long term blood pressure improvement in atherosclerotic and mixed series[20,23,26,27,40]. The present results showed that 53 per cent of the patients were cured or improved at the end of follow-up. After a total of five repeated treatments with PTRA and four revisional surgical procedures in eight patients, the results are among the best reported with a 90 per cent long term blood pressure improvement. Secondary results are usually not reported in the literature although they give a better description of the clinical situation.

Costs

Preprocedure preparation and diagnostic measures, and thus the costs of these, were similar in both groups, representing around a third of the total treatment costs. This seems to be proportionally rather large, but we have chosen to make a great effort to establish properly the diagnosis of renovascular hypertension. Thus, all patients were evaluated in hospital for 1 week. If possible, all antihypertensive drugs were withdrawn and a standardized intake of sodium established in order to achieve a proper evaluation of the hypertension and measurements of renal vein renin. England *et al.*[7] found that the preoperative evaluation was 60 per cent more expensive compared with predilatation evaluation, and in their study the preprocedure costs were less than a quarter of the total costs.

In the present series the procedure costs were 5·7 times higher for surgical treatment than for PTRA. In the study by England surgery was also more expensive, but only by a factor of 2·6 times. Their figures probably also include postprocedure costs. Adding up our procedure and postprocedure costs, our revascularization costs are 2·9 times higher for surgery, i.e. similar to those described by England. Postprocedure costs in the present series were, as expected, higher in the surgical group than in the PTRA group, mainly due to longer hospital stay. These costs could not be directly compared with any corresponding costs in the study by England[7]. Follow-up, on the other hand, was much more expensive in the PTRA group than in the surgically treated group, 40 per cent and 8 per cent, respectively, of the total costs. This is due to the recurrences which require additional revascularization and more frequent outpatient visits for control of blood pressure. Thus, PTRA follow-up costs were four times higher than the surgical follow-up costs (a direct comparison with the results of England *et al.* is not possible as regards follow-up costs). The total cost for achieving 100 per cent patency and 90 per cent blood pressure response in the PTRA group was around 90 per cent of the total costs in the surgical group. This differs from the findings of England *et al.* who, on average, showed costs for surgery nearly twice as high as those for PTRA.

Concluding remarks

The present results are technically and clinically consistent with those of other studies, both of surgically and of PTRA-treated patients. The cost of treating renal artery stenosis causing renovascular hypertension, to achieve a good primary and secondary patency and blood pressure control, were similar regardless of whether PTRA or surgery was chosen as the initial treatment. Neither from the clinical nor from the economic view point should the methods be regarded as competitive, but rather as complementary. For initial therapy PTRA should be chosen, and surgery used if PTRA fails. With this strategy, about 50 per cent of patients can be adequately treated with a single PTRA procedure and the other 50 per cent will need complementary intervention, i.e. rePTRA or surgery. Costs could probably, with this strategy, be kept on the lowest level possible. The present series was too small to warrant a more sophisticated economic analysis than direct costs but the method is simple and convenient for non-economists such as clinicians.

Acknowledgements

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References

1. Grüntzig A, Kuhlman U, Vetter W, Lulolf K, Mayer B, Siegenthaler W. Treatment of renovascular hypertension with percutaneous transluminal dilatation of a renal artery stenosis. *Lancet* 1978; **i**: 801–2.
2. Weibull H, Bergqvist D, Jonsson K, Carlsson S, Takolander R. Analyses of complications after percutaneous transluminal angioplasty of renal artery stenosis. *Eur J Vasc Surg* 1987; **1**: 77–84.
3. Bergqvist D, Jonsson K, Weibull H. Complications after percutaneous transluminal angioplasty of peripheral and renal arteries. *Acta Radiol* 1987; **28**: 3–12.
4. Luft F, Grim C, Weinberger M. Intervention in patients with renovascular hypertension and renal insufficiency. *J Urol* 1983; **130**: 654–6.
5. Tegtmeyer CJ, Kofler TJ, Ayers CA. Renal angioplasty: current status. *AJR* 1984; **142**: 17–21.
6. Kremer Hovinga TK, de Jong PE, de Zeeuw D, Donker AJM, Schuur KH, van der Hem GK. Restenosis prevalence and long-term effects on renal function after percutaneous transluminal renal angioplasty. *Nephron* 1986; **44**(Suppl 1): 64–7.
7. England WL, Roberts SD, Grim CE. Surgery or angioplasty for cost-effective renal revascularization? *Med Decis Making* 1987; **7**: 84–91.
8. Andersson I, Bergentz S-E, Eriksson BR, Dymling JF, Hansson BG, Hökfeldt B. Unilateral renal artery stenoses and hypertension II. Angiographic findings correlated with blood pressure response after surgery. *Acta Radiol* 1979; **20**: 895–906.
9. Drummond MF, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes*. Oxford: Oxford University Press, 1987.
10. Stoddart GL, Drummond MF. How to read clinical journals: VII. To understand an economic evaluation (part B). *Can Med Assoc J* 1987; **130**: 1542–9.
11. Bergqvist D, Jendteg S, Lindgren B. Standard for the cost-benefit approach to vascular surgery. *Acta Chir Scand* 1990; **Suppl 555**: 105–10.
12. Pohl MA, Novick AC. Natural history of atherosclerotic and fibrous renal artery disease: clinical implications. In: Porush JG *et al.*, eds. *Hypertension and the Kidney. Proceedings of a Symposium*. Orlando: Grune & Stratton Inc, 1985: 120–3.
13. Stanley JC, Fry WJ. Renovascular hypertension secondary to arterial fibrodysplasia in adults. *Arch Surg* 1975; **110**: 922–8.
14. Sos TA, Pickering TG, Phil D *et al.* Percutaneous transluminal renal angioplasty in renovascular hypertension due to atheroma or fibromuscular dysplasia. *N Engl J Med* 1983; **309**: 274–9.
15. Geyskes GG, Puylaert, Oei HY *et al.* Follow-up study of 70 patients with renal artery stenosis treated by percutaneous transluminal dilatation. *Br Med J* 1983; **287**: 333–6.
16. Tegtmeyer CJ, Kellum CD, Ayers C. Percutaneous transluminal angioplasty of the renal artery. *Radiology* 1984; **153**: 77–84.
17. Miller GA, Ford KK, Braun SD *et al.* Percutaneous transluminal angioplasty *vs* surgery for renovascular hypertension. *AJR* 1985; **450**: 7.
18. Kuhlman U, Greminger P, Grüntzig A *et al.* Long-term experience in percutaneous transluminal dilatation of renal artery stenosis. *Am J Med* 1985; **79**: 692–8.
19. Martin LG, Pric RB, Casarella WJ *et al.* Percutaneous angioplasty in clinical management of renovascular hypertension: initial long-term results. *Radiology* 1985; **155**: 629–33.
20. Grim CE, Yune HY, Donohue JP, Weinberger MH, Dilley R, Klatte EC. Renal vascular hypertension. Surgery *vs* dilatation. *Nephron* 1986; **44**(Suppl 1): 96–100.
21. Simonetti G, Urigo F, Sergiacomi GL *et al.* Percutaneous transluminal renal angiography. Follow-up at 48 months. In: Glorioso N, Laragh JH, Rapelli A *et al. Renovascular Hypertension*. New York: Raven, 1987: 499–509.
22. Bell GM, Reid J, Buist TAS. Percutaneous transluminal angioplasty improves blood pressure and renal function in renovascular hypertension. *Q J Med* 1987; **241**: 393–403.
23. Geyskes GG. Treatment of renovascular hypertension with percutaneous transluminal renal angioplasty. *Am J Kidney Dis* 1988; **12**: 253–65.
24. Brawn LA, Ramsay LE. Is improvement real with percutaneous transluminal angioplasty in the managment of renovascular hypertension? *Lancet* 1987; **ii**: 1313–16.
25. Martin LG, Casarella WJ, Alspaugh JP, Chuang VP. Renal artery angioplasty: increased technical success and decreased complications in the second 100 patients. *Radiology* 1986; **159**: 631–4.
26. Zabbo A, Novick AC. Digital subtraction angiography for non-invasive imaging of the renal artery. *Urol Clin North Am* 1984; **11**: 409–16.
27. Schwarten DE. Transluminal angioplasty of renal artery stenosis: 70 experiences. *AJR* 1980; **135**: 969–74.
28. Colapinto RF, Stronell RD, Harries-Jones EP *et al.* Percutaneous transluminal dilatation of the renal artery: follow-up studies on renovascular hypertension. *AJR* 1982; **139**: 727–32.
29. Katzen BT, Chang J, Know WG. Percutaneous transluminal angioplasty with the Grüntzig balloon catheter. A review of 70 cases. *Arch Surg* 1979; **114**: 1389–99.
30. Puijlaert CBAJ, Boomsma JHB, Ruijs JHJ *et al.* Transluminal renal artery dilatation in hypertension: technique, results, and complications in 60 cases. *Urol Radiol* 1981; **2**: 201–10.
31. Sos TA, Saddekni S, Sniderman KW *et al.* Renal artery angioplasty: techniques and early results. *Urol Radiol* 1982; **3**: 223–31.
32. Perry MO, Silane MF. Management of renovascular problems during aortic operations. *Arch Surg* 1984; **119**: 681–5.
33. Dean RH, Hollifield JW, Oates JA. Medical versus surgical treatment of renovascular hypertension. In: Stanley JC, Ernst CB, Fry WJ, eds. *Renovascular Hypertension*. Philadelphia: WB Saunders, 1984: 354–62.
34. Dean RH. Aortorenal bypass for renovascular hypertension due to atherosclerosis. In: Rutherford RB, ed. *Vascular Surgery*. 2nd ed. Philadelphia: WB Saunders, 1984: 1136–44.
35. Novick AC, Ziegelbaum M, Vidt DG, Gifford RW Jr, Pohl MA, Goormastic M. Trend in surgical revascularization for renal artery disease. *JAMA* 1987; **257**: 498–501.
36. Fowl RJ, Hollier LH, Berntz PE, Pairolero PC, Vogt PA, Cherry KJ. Repeat revascularization versus nephrectomy in the treatment of recurrent renovascular hypertension. *Surg Gynecol Obstet* 1986; **162**: 37–42.
37. Dean RH, Krueger TC, Whiteneck JM *et al.* Operative management of renovascular hypertension. Results after a follow-up of fifteen to twenty-three years. *J Vasc Surg* 1984; **1**: 234–42.
38. Bergqvist D, Weibull H, Bergentz S-E. Acute necrotizing pancreatitis complicating surgery for renovascular hypertension. *Acta Chir Scand* 1989; **155**: 498–92.
39. Stanley JC, Ernst CB, Fry WJ. Surgical treatment of renovascular hypertension: results in specific patient subgroups. In: Stanley JC, Ernst CB, Fry WJ, eds. *Renovascular Hypertension*. Philadelphia: WB Saunders, 1984: 363–71.
40. Vidt DG. Geriatric hypertension of renovascular origin: diagnosis and managment. *Geriatrics* 1987; **42**: 59–68.

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Haemodynamic significance of incompetent calf perforating veins

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A total of 149 consecutive unselected patients (221 limbs) who presented with signs and symptoms of chronic venous problems (varicose veins with or without ankle oedema, skin changes and leg ulcers) have been studied by clinical examination, ascending deep to superficial venography, Doppler ultrasound and ambulatory venous pressure measurements. Of the limbs, 180 (82 per cent) had varicose veins without obstruction in the deep veins or reflux in the popliteal or femoral veins while 41 (18 per cent) had deep venous disease. Of the 180 limbs with 'primary' varicose veins 110 (60 per cent) did not have incompetent calf perforating veins (group A) while 70 (40 per cent) did (group B). On the basis of the ambulatory venous pressure after calf muscle exercise and the refilling time, the incompetent calf perforating veins of limbs in group B belonged to three subgroups of different haemodynamic significance. In 20 limbs (30 per cent) they were found to be of no haemodynamic significance, in 25 (35 per cent) of moderate haemodynamic significance and in 25 (35 per cent) of major haemodynamic significance. The last were, on clinical examination, indistinguishable from limbs with deep venous disease although they had patent deep veins with competent popliteal valves.

Although the adverse effect of incompetent calf perforating veins (ICPV) in limbs with reflux and/or obstruction of the deep venous system is well established[1–5], the finding of ICPV in patients with varicose veins in the presence of patent deep veins with competent valves is of unknown haemodynamic significance[3,6–10]. The purpose of this study was to identify the proportion of patients with varicose veins that have ICPV and to assess the haemodynamic effect of the latter.

Patients and methods

Patients

A total of 221 diseased limbs of 149 consecutive unselected patients who presented with symptoms and signs of a chronic venous condition of the lower limbs (varicose veins with or without ankle oedema, skin changes and leg ulcers) have been studied by clinical examination, ascending deep to superficial functional venography, continuous wave Doppler ultrasound and ambulatory venous pressure measurements.

Ascending deep to superficial functional venography

A 21 Fr gauge butterfly needle was inserted in a vein on the dorsum of the foot with the screening table tilted 60° (legs down). Non-ionic contrast medium, meglumine sodium ixoaglate 320 (Hexabrix 320, Rhone-Poulenc Ltd., Dagenham, UK) was injected. It was directed into the deep veins by a narrow (2·5 cm) pneumatic cuff at the ankle which occluded the superficial veins. Contrast medium was observed to ascend in the deep veins and to flow to the superficial veins through incompetent perforating veins.

Reflux in the short and long saphenous veins if not seen spontaneously was demonstrated by manual calf compression and release when the contrast medium had reached the saphenopopliteal and saphenofemoral junctions. Finally, the contrast medium was visualized in the pelvic veins and inferior vena cava. Up to a total of 120 ml of contrast medium was injected. The aim of this investigation was to establish the patency of the deep veins and their appearance (normal or abnormal) as well as to document the presence and sites of deep to superficial reflux.

Doppler ultrasonography

All patients were examined with Doppler ultrasound (Parks model 801, Parks Medical Electronics, Aloka, Oregon, USA) using an 8 MHz probe for reflux in the long and short saphenous and popliteal veins[4,11,12]. The examination was performed with the patient standing[13].

Ambulatory venous pressure measurements

All patients were studied with ambulatory venous pressure measurements to evaluate the functional status of the superficial and deep venous system[4,9,12–15]. A vein on the dorsum of the foot was cannulated with a 21 Fr gauge butterfly needle which was connected to a pressure transducer and pen recorder. The patient initially stood still, supporting himself by holding on to a frame which prevented any involuntary leg muscle contractions and ensured a stable pressure recording of the resting venous pressure (P_0).

The patient then performed a standard exercise of ten tiptoe movements at a rate of one per second. After completion of the exercise the patient remained standing and the return of the venous pressure to the resting level was recorded. The lowest pressure (P) reached during exercise and the time required for the postexercise pressure to return to 90 per cent of the final resting pressure, i.e. 90 per cent recovery time (90 per cent RT), which is more precisely defined than the end point of full recovery[16] (*Figure 1*), were obtained. The exercise was then repeated with a 2·5 cm wide pneumatic cuff applied just below the knee to eliminate possible reflux from the long and short saphenous veins (*Figure 2*). Finally, the patient repeated the same exercise with a cuff applied at the ankle to eliminate the effect of reflux in the superficial system of veins and incompetent perforating veins.

Criteria for classifying limbs into groups A, B and C

Group A: limbs with varicose veins and no incompetent calf perforating veins. Limbs were classified into this group if they were found to have varicose veins, reflux in the long and/or short saphenous vein on Doppler ultrasonography and on venography, patent deep veins as shown by venography with competent popliteal valves on Doppler ultrasonography, an ambulatory venous pressure (P) that was less than 45 mmHg when the below knee tourniquet was inflated and no venographic evidence of incompetent calf perforating veins. Previous work has demonstrated that, in the presence of competent popliteal valves and a below knee or ankle tourniquet, P is practically always less than 45 mmHg. It is always higher than 45 mmHg in the presence of popliteal reflux[4].

Group B: limbs with varicose veins and incompetent calf perforating veins. Limbs were classified into this group if they were found to have varicose veins, reflux in the long and/or short saphenous vein on

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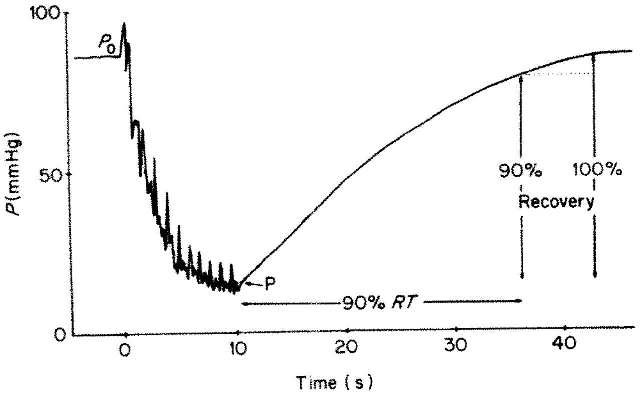

Figure 1 *Recording of the venous pressure in the foot of a limb with normal venous system during ten tiptoe movements and during the recovery phase. P_0, Initial resting pressure with the patient standing still; P, the lowest pressure reached; 90%RT, the time taken for the pressure to rise to 90% of the final resting pressure*

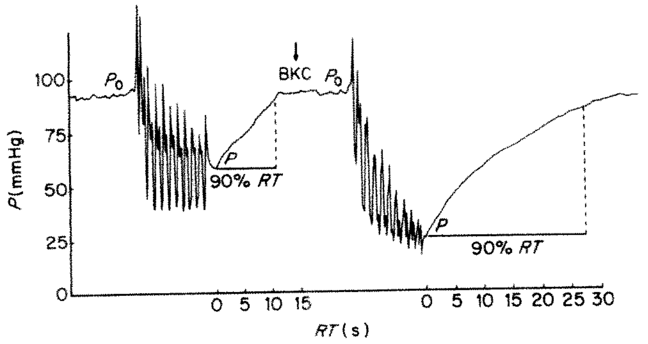

Figure 2 *Recording of the venous pressure in the foot of a limb with varicose veins but without incompetent calf perforating veins, before and after the application of a below knee cuff (BKC). Note normalization of both the lowest pressure reached (P) and 90%RT (recovery time) when the exercise was repeated with the application of a below knee cuff*

Doppler ultrasonogrphy and on venography, patent deep veins as shown by venography with competent popliteal valves on Doppler ultrasonography, an ambulatory venous pressure that was less than 45 mmHg when the ankle tourniquet was inflated and venographic evidence of incompetent calf perforating veins.

Group C: limbs with deep venous disease. Limbs were classified into this group if they were found to have obstruction as demonstrated by venography, incompetent popliteal valves (popliteal reflux) detected by Doppler ultrasonography, venography and an ambulatory venous pressure at the end of exercise (*P*) that was greater than 45 mmHg even when the ankle tourniquet was inflated.

The values of the ambulatory venous pressure, *P*, and the 90 per cent *RT* measured without and with a cuff below the knee or at the ankle were used to classify limbs of group B into three further subgroups of different haemodynamic significance: I, II and III (see Results).

Results

Of the 221 limbs studied, 180 (82 per cent) were classified in groups A and B, i.e. they had 'primary' varicose veins. In these limbs the deep veins were patent and the popliteal valves were competent. The remaining 41 limbs (18 per cent) were classified in group C, i.e. they had deep venous disease (*Figure 3*).

Of the 180 limbs with 'primary' varicose veins 110 were in group A and 70 in group B. Application of a below knee or ankle tourniquet to control reflux in the long and short saphenous veins in the limbs of group A always resulted in *P* less than 45 mmHg and 90 per cent *RT* greater than 15 s (i.e. values found in normal limbs without the application of any tourniquet[15]).

In limbs with deep venous insufficiency (group C), *P* was greater than 50 mmHg and 90 per cent *RT* shorter than 10 s even with the application of a below knee or ankle tourniquet.

By plotting the values of the ambulatory venous pressure *P* against the 90 per cent *RT* (*Figures 4–6*) without and with a cuff below the knee or at the ankle it became possible to classify limbs of group B into three subgroups (I, II, III) indicating the different haemodynamic significance of the incompetent perforating veins.

Subgroup I consisted of 20 limbs which had a 90 per cent *RT* less than 15 s with/without *P* greater than 45 mmHg without the application of a tourniquet, but in whom after the application of a below knee tourniquet *P* became less than 45 mmHg and 90 per cent *RT* greater than 15 s, i.e. normal (*Figure 4*). These limbs behaved like limbs with 'primary' varicose veins of group A which did not have any incompetent calf perforating veins demonstrable on venography. Thus, the incompetent perforating veins of the limbs of group I demonstrated on venography could be considered to be of no haemodynamic significance.

Subgroup II consisted of 25 limbs which had a 90 per cent *RT* less than 15 s with or without a *P* greater than 45 mmHg without the application of a tourniquet. These values did not become normal with the application of a below knee tourniquet,

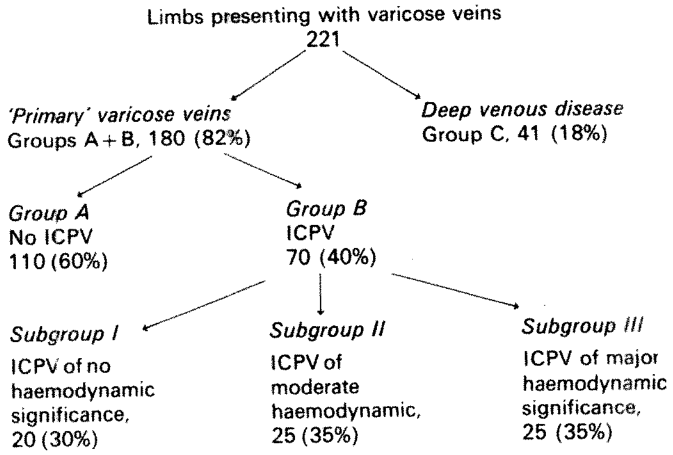

Figure 3 *The proportion of limbs classified in groups A, B, C, and subgroups I, II and III. ICPV, incompetent calf perforating veins*

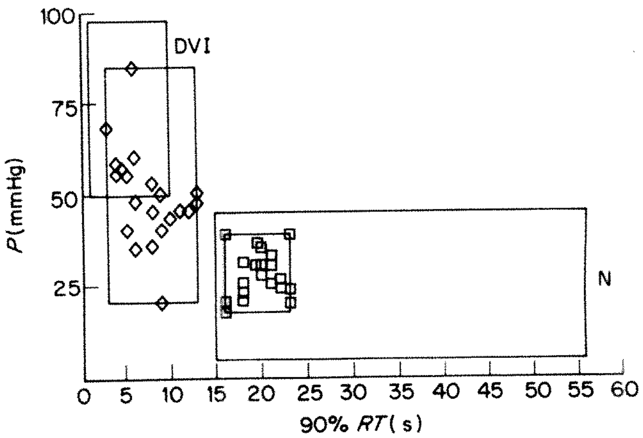

Figure 4 *Plot of P (pressure) against 90%RT (recovery time) for incompetent calf perforators, group I. Rectangle DVI (deep venous insufficiency) marks the range of P and 90%RT in limbs with deep venous valvular incompetence. Rectangle N marks the range of P and 90%RT in limbs with a normal venous system (from previous studies). Each point represents an individual result of a limb with incompetent calf perforating veins of no haemodynamic significance (subgroup I). There was no need to apply an ankle cuff since normalization of the results was achieved with a below knee cuff. ◇, No cuff; □, below knee cuff; ○, ankle cuff*

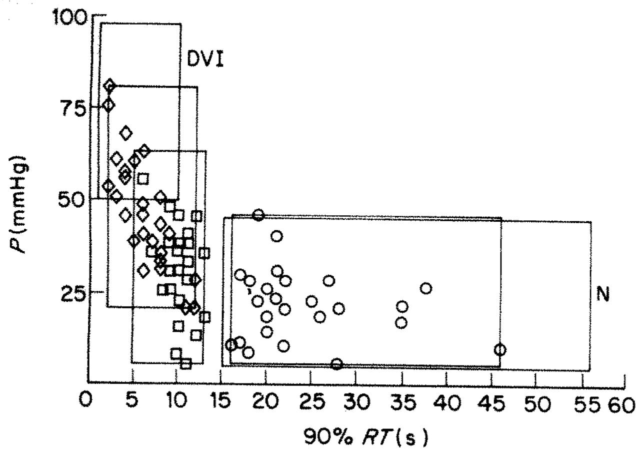

Figure 5 *Plot of P (pressure) against 90%RT (recovery time) for incompetent calf perforators, group II. Rectangle DVI (deep venous insufficiency) marks the range of P and 90%RT in limbs with deep venous valvular incompetence. Rectangle N marks the range of P and 90%RT in limbs with a normal venous system (from previous studies). Diamonds represent individual results of limbs with incompetent calf perforating veins of moderate haemodynamic significance (subgroup II).* ◇, *No cuff;* □, *below knee cuff;* ○, *ankle cuff*

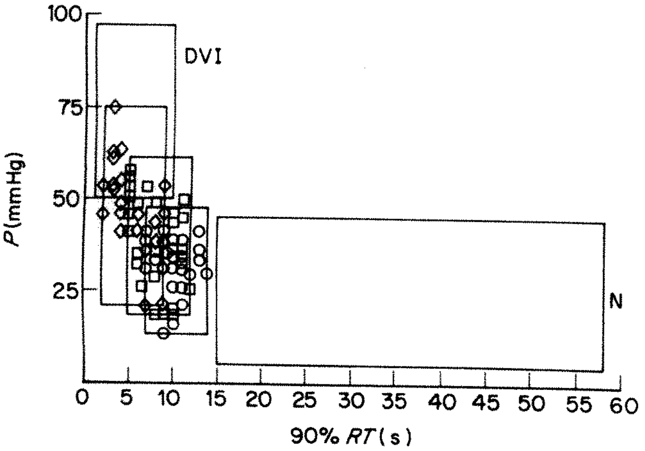

Figure 6 *Plot of P (pressure) against 90%RT (recovery time) for incompetent calf perforators, group III. Rectangle DVI (deep venous insufficiency) marks the range of P and 90%RT in limbs with deep venous valvular incompetence. Rectangle N marks the range of P and 90%RT in limbs with a normal venous system (from previous studies). Diamonds represent individual results of limbs with incompetent calf perforating veins of severe haemodynamic significance (subgroup III).* ◇, *No cuff;* □, *below knee cuff;* ○, *ankle cuff*

but did (i.e. >15 s and <45 mmHg respectively) with an ankle tourniquet (*Figure 5*). The incompetent perforating veins of these limbs were considered to be of moderate haemodynamic significance.

Subgroup III consisted of 25 limbs which had a 90 per cent RT less than 15 s with or without a P greater than 45 mmHg without the application of a tourniquet. These values did not become normal with the application of a below knee tourniquet, but the application of the ankle tourniquet reduced P to 45 mmHg or less although 90 per cent RT remained less than 15 s (*Figure 6*). In view of the short 90 per cent RT despite the ankle tourniquet the incompetent perforating veins of these limbs were considered to be of major haemodynamic significance.

The incidence of skin changes and/or ulceration in each of the three subgroups I, II and III is shown in *Table 1*. There was a high incidence of liposclerosis in subgroups II and III and of ulceration in subgroup III.

Discussion

In the past, several workers have tried to determine the importance of ICPV in association with varicose veins, skin changes and venous ulceration[2,5,6,14,17–20]. Despite the availability of many different methods for detection of ICPV[21–24], there is still controversy about the haemodynamic significance of the ICPV in patients with competent popliteal valves in the deep venous system. It has even been stated that ICPV do no contribute to the venous hypertension at all, especially in patients with superficial venous incompetence only[25]. Most of the controversies can be attributed to the difficulties in the ability to detect and grade quantitatively the contribution of the ICPV to the venous hypertension and its clinical manifestations. It is therefore not surprising that there are many different concepts about the need and way to treat this condition[3,6–10]. However, in the present study, it was possible to demonstrate that there are three haemodynamically different groups of incompetent calf perforating veins and this finding may explain many of the existing controversies.

We have found that some of the ICPV contribute significantly to the venous hypertension by producing a short refilling time (90 per cent RT). In this we disagree with the work of others, who have stated that ambulatory venous hypertension at the ankle and the recovery time are always normalized by proximal occlusion of the long or short saphenous trunk, even in patients with large incompetent perforating veins at the lower calf[6,25,26]. In the present study, this held true only for 30 per cent of such patients, i.e. those who fell into subgroup I.

The findings in the patients in subgroup II and subgroup III document clearly the importance and clinical significance of the ICPV by their effect on the recovery time and thus on the venous hypertension. The clinical differences in the appearance of the three subgroups support this (*Table 1*). Patients who have very rapid refilling time during the calf muscle relaxation period will have a high mean ambulatory venous pressure throughout the day. This is because, when walking at a slow pace of 1–2 km per hour, the venous pressure when the foot is lifted off the ground will reach a high level before the next step, i.e. the next calf muscle contraction.

The present findings have important clinical implications for the management of patients with ICPV and skin changes. From a practical point of view it could be useful to exclude deep venous disease which would not be amenable to present surgical procedures. The clinical appearance of group III, apart from the minimal or absent oedema, could easily be mistaken for that of a postphlebitic limb, and yet the deep veins are patent and the popliteal valves are competent. Many such patients who, because of leg skin changes and ulceration, were previously labelled as having postphlebitic limbs should be amenable to successful surgical intervention and/or successful injection sclerotherapy.

The results obtained in this study can be explained on the basis of the following hypothesis. The abnormality of limbs of subgroup I is as follows: incompetent perforating veins with competent valves in the deep veins. The flow in the superficial veins is downward with outward flow in the incompetent perforating veins during calf compression and inward flow during calf relaxation (*Figure 7a*). The net effect in the

Table 1 *Incidence of skin changes (i.e. 'eczema', pigmentation and liposclerosis) and ulceration*

	Skin changes	Leg ulcers	Total no. of limbs
Subgroup I	0 (0)	0 (0)	20
Subgroup II	17 (68)	0 (0)	25
Subgroup III	25 (100)	7 (28)	25

Values in parentheses are percentages

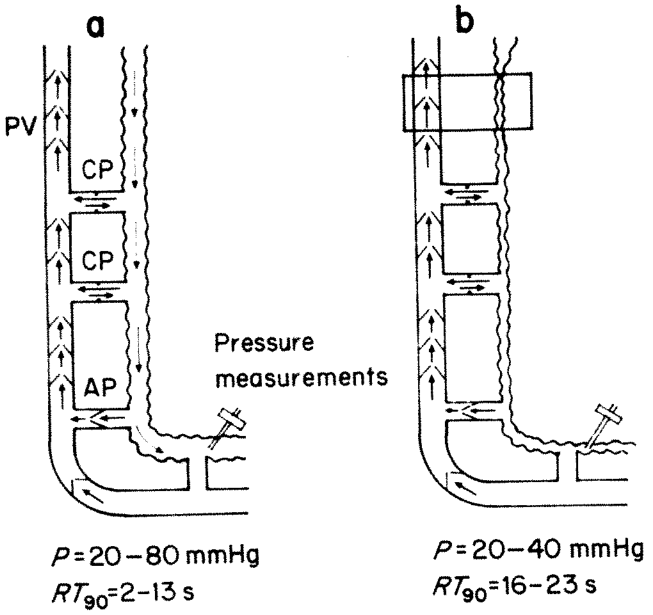

Figure 7 *The haemodynamics of subgroup I explained on the basis of anatomical abnormality. PV, Popliteal valves; CP, calf perforating veins; AP, ankle perforating vein*

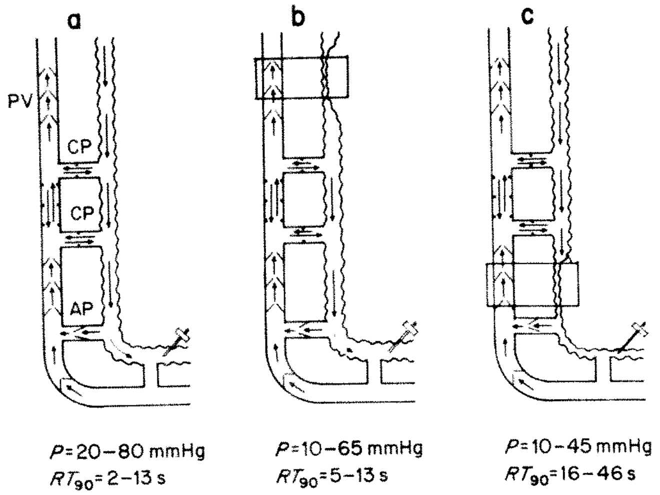

Figure 8 *The haemodynamics of subgroup II explained on the basis of anatomical abnormality. PV, Popliteal valves; CP, calf perforating veins; AP, ankle perforating vein*

incompetent perforating veins is inwards due to the competent valves in the deep veins just above and below the junction with the perforating veins. The ambulatory venous pressure is in the range of 20–80 mmHg (*Figure 4*) and 90 per cent *RT* is 2–13 s depending on the amount of reflux in the superficial veins of the long and/or short saphenous system. Application of a below knee tourniquet (*Figure 7b*) will abolish reflux in the superficial system whose veins will collapse normalizing *P* and 90 per cent *RT*. Only a little of the blood that is pumped up the deep veins will reflux into the superficial veins.

The abnormality in limbs of subgroup II is as follows: incompetent perforating veins with a considerable number of incompetent valves in the deep veins above and below the junction with the incompetent perforating veins (*Figure 8a*), but with competent deep valves in the lower part of the leg (at and just proximal to the ankle) and at the popliteal region. In these limbs a considerable amount of blood leaks from deep to superficial through the incompetent perforating veins. Application of the below knee tourniquet (*Figure 8b*) abolishes the amount of reflux in the long and short saphenous veins, but not that leaking out through the calf perforating veins. *P* and 90 per cent *RT* (*Figure 5*) are reduced but not normalized. However, the application of the ankle tourniquet (*Figure 8c*) prevents any deep to superficial perforator reflux or reflux down the superficial veins to reach the foot. The veins of the foot collapse with normalization of *P* and 90 per cent *RT* (*Figure 5*).

The abnormality in limbs of subgroup III is more severe: all valves in the deep veins distal to the popliteal are incompetent including those at the ankle. There is a large amount of blood refluxing from deep to superficial through a large number of incompetent perforating veins including those at the ankle (*Figure 9a*). Application of the below knee tourniquet abolishes the downward flow in the long and short saphenous system but not that leaking through the perforating veins of the calf and ankle (*Figure 9b*). *P* and 90 per cent *RT* are only moderately affected (*P* more than 90 per cent *RT*) depending on the volume ejected by the calf muscle pump through the competent popliteal valves (*Figure 6*). Application of the ankle tourniquet abolishes reflux to the foot via the superficial veins but not through the deep, via the lowest incompetent ankle perforating veins (*Figure 9c*). *P* normalizes (<45 mmHg) during exercise because the outflow from the foot markedly exceeds the inflow (reflux). However, in view of the reflux along the pathway shown in *Figure 9c* at the end of the exercise the refilling time (90 per cent *RT*) remains short (7–14 s) (*Figure 6*).

Support for this hypothesis is available not only from the findings of the present study but from the work of others: Bjordal's studies of flow and direction of flow at rest and during exercise in the perforating and superficial veins obtained simultaneously with pressure measurements[25], recent studies with duplex scanning which indicate that reflux in the deep veins may be of varied extent and in many patients can be confined to only limited regions[25], and the work of Moore and colleagues[27] on the distribution of venous valvular incompetence in patients with post-thrombotic syndrome.

Conclusive proof of this hypothesis may be possible by repeating the present study with ultrasonic colour flow imaging that has now become available. This has now made possible the detection of reflux and of its extent in the tibial, peroneal and perforating veins.

Obviously patients with ICPV may, with time, deteriorate both in their clinical course and their haemodynamics, thus moving from subgroups I/II to subgroups II/III. Thus, future work should identify patients of group B and subgroups I–III and study the long term results of treatment. It is particularly important to study the clinical effect of ligation or compression sclerotherapy of the incompetent calf perforating veins in limbs of group III and group C. In the past a distinction between these

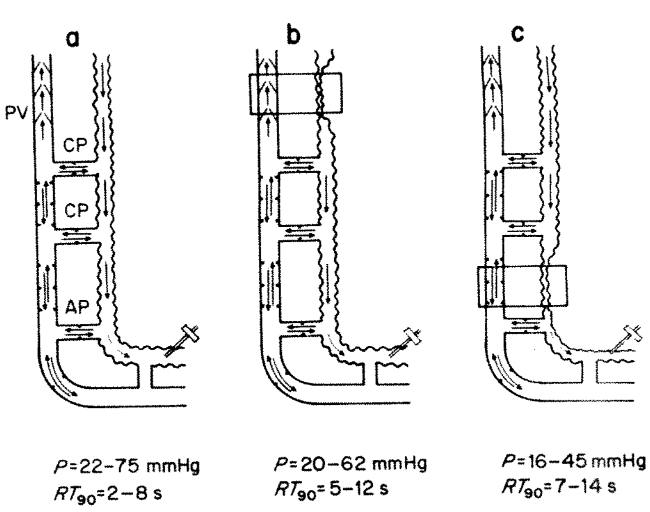

Figure 9 *The haemodynamics of subgroup III explained on the basis of anatomical abnormality. PV, Popliteal valves; CP, calf perforating veins; AP, ankle perforating vein*

groups could not be made and this may explain the controversy that exists about and the variable results found after subfascial ligation[3].

References

1. Burnand KG, Browse NL. The postphlebitic leg and venous ulceration. In: Russel RCG, ed. *Recent Advances in Surgery*, No. 11. Edinburgh: Churchill Livingstone, 1982: 225–46.
2. May R, Partsh J, Straubesand J. *Perforating Veins*. 1st ed. Urban & Schwarzenberg, 1981.
3. Negus D, Friedgood A. The effective management of venous ulceration. *Br J Surg* 1983; **70**: 623–7.
4. Shull KC, Nicolaides AN, Fernandes e Fernandes J *et al.* Significance of popliteal reflux in relation to ambulatory venous pressure and ulceration. *Arch Surg* 1979; **114**: 1304–6.
5. Sumner DS. Venous dynamics – varicosities. *Clin Obstet Gynecol* 1981; **24**: 743–60.
6. Burnand KG, O'Donnell TF, Thomas ML, Browse NL. The relative importance of incompetent communicating veins in the production of varicose veins and venous ulcers. *Surgery* 1977; **82**: 9–14.
7. Linton RR. The communicating veins of the lower limb and operating technique for their ligation. *Ann Surg* 1983; **107**: 582–93.
8. Hobbs JT. The treatment of varicose veins by sclerosing therapy. In: Rutherford R, ed. *Vascular Surgery*. 2nd ed. Philadelphia: WB Saunders, 1984: 1332–47.
9. Nicolaides AN, Hoare M, Miles CR *et al.* Value of ambulatory venous pressure in the assessment of venous insufficiency. *Vasc Diag Ther* 1981; **3**: 41–5.
10. Wilkinson GE, Maclaren IF. Long term review of procedures for venous perforator insufficiency. *Surg Gynecol Obstet* 1986; **163**: 117–20.
11. Folse R, Alexander RH. Directional flow detection for localising venous valvular incompetence. *Surgery* 1970; **67**: 114–21.
12. Lewis JD, Parson DCS, Needham T. The use of venous pressure measurements and directional Doppler recordings in distinguishing between superficial and deep valvular incompetence in patients with deep venous insufficiency. *Br J Surg* 1973; **60**: 312 (Abstract).
13. Nicolaides AN, Christopoulos D, Vasdekis S. Progress in the investigation of chronic venous insufficiency. *Ann Vasc Surg* 1989; **3**: 278–92.
14. Nicolaides AN, Zukowski AJ, Lewis R, Kyprianou P, Malouf GM. Venous pressure measurements in venous problems. In: Bergan JJ, Yao JST, eds. *Surgery of the Veins*. Orlando: Grune & Stratton Inc, 1985: 111–19.
15. Hoare MC, Nicolaides AN, Miles CR *et al.* The role of primary varicose veins in venous ulceration. *Surgery* 1982; **92**: 450–53.
16. Nicolaides AN, Miles C. Photoplethysmography in the assessment of venous insufficiency. *J Vasc Surg* 1987; **5**: 404–12.
17. Burnand KG, Whimster IW, Clemenson G, Thomas ML, Browse NL. The relationship between the number of capillaries in the skin of the venous ulcer bearing area of the lower leg and the fall in the foot vein pressure during exercise. *Br J Surg* 1981; **68**: 297–300.
18. Strandness DE, Sumner DS. *Haemodynamics for Surgeons*. 1st ed. New York: Grune and Stratton, 1975: 396–410.
19. Fegan WG, Kline AL. The cause of varicosity in superficial veins of the lower limb. *Br J Surg* 1972; **59**: 798.
20. Fegan WG. Varicose veins and chronic venous insufficiency. *Practitioner* 1970; **204**: 555.
21. O'Donnell TF, Burnand KG, Clemenson G, Thomas ML, Browse NL. Doppler examination vs. clinical phlebographic detection of the location of incompetent perforating veins. *Arch Surg* 1977; **112**: 31–5.
22. Miller SS, Grossman JA, Foote AV. The ultrasonic detection of incompetent perforating veins. *Br J Surg* 1971; **58**: 872 (Abstract).
23. Patil KD, Williams JR. Thermographic localisation of incompetent perforating veins in the leg. *Br Med J* 1970; **1**: 195–7.
24. Wojciechowski J, Holm J, Zachrisson BF. Thermography and phlebography in the detection of the incompetent perforating veins. *Acta Radiol Diag* 1982; **23**: 199–201.
25. Bjordal RI. Pressure patterns in the saphenous system in patients with venous leg ulcers. *Acta Chir Scand* 1971; **137**: 495–501.
26. Szendro G, Nicolaides AN, Zukowski AJ *et al.* Duplex scanning in the assessment of deep venous incompetence. *J Vasc Surg* 1986; **4**: 237.
27. Moore DJ, Himmel PD, Sumner DS. Distribution of venous valvular incompetence in patients with post-phlebitic syndrome. *J Vasc Surg* 1986; **3**: 49.

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Surgical workshop

Br. J. Surg. 1991, Vol. 78, May, 630–631

Subclavian-to-subclavian bypass facilitated by the use of an interposition vein cuff

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Occlusion or severe stenosis of the first part of the subclavian artery proximal to the origin of the vertebral artery may give rise to the signs and symptoms of the subclavian steal syndrome. These encompass vertebrobasilar ischaemia in association with arm claudication, unequal or absent radial pulses and a decreased blood pressure in the affected limb[1]. If the symptoms are severe, a subclavian-to-subclavian bypass is one of the options available. Because of the fragility of the subclavian artery, this can be a difficult procedure, particularly if a polytetrafluoroethylene (PTFE) graft is used. To make the procedure safer and easier a Miller type vein cuff may be interposed between the graft and the artery.

Surgical technique

A 68-year-old man with right subclavian steal syndrome was admitted for subclavian-to-subclavian bypass. Assessment included arch aortography which demonstrated complete occlusion of the right subclavian artery proximal to the vertebral artery and a moderate stenosis of the right internal carotid artery. The right radial pulse was impalpable and the blood pressure was diminished in the right arm.

Under general anaesthesia both subclavian arteries were exposed using a supraclavicular approach. The phrenic nerves were identified and access to the proximal subclavian arteries gained by dividing the scalenus anterior muscles. Both subclavian arteries were controlled and then opened by longitudinal arteriotomies. A 10 cm segment of long saphenous vein was dissected from the ankle and used to fashion two vein cuffs, which were anastomosed to the subclavian arteries using continuous 6/0 polypropylene sutures. A 6 mm reinforced PTFE graft was tunnelled anterior to the common carotid arteries and posterior to the sternomastoid muscles. The graft was anastomosed at either end to the vein cuffs using continuous 6/0 Gore-Tex® sutures (W.L. Gore and Associates, Woking, UK) (*Figure 1*).

After operation, blood pressure was equal in both arms. Duplex scanning showed that the graft was patent at discharge, 1 week after operation (*Figure 2*).

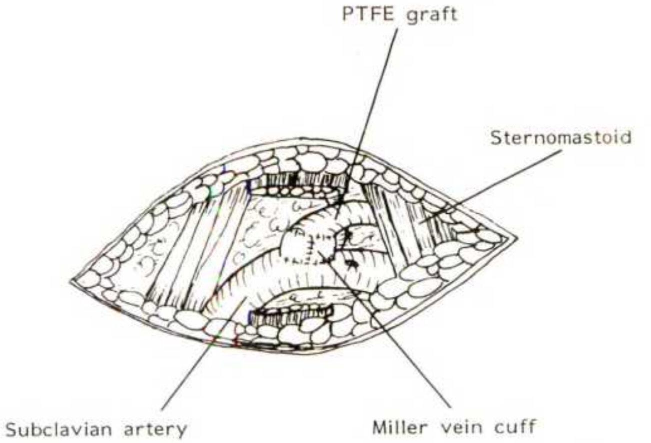

Figure 1 *Miller type vein cuff facilitating subclavian-to-subclavian crossover graft. PTFE, polytetrafluoroethylene*

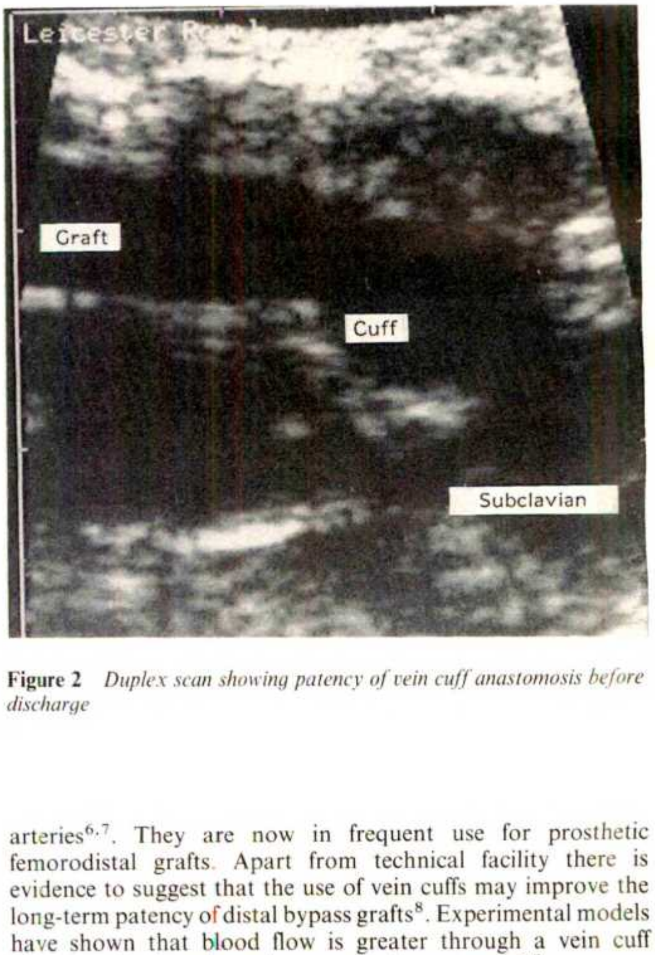

Figure 2 *Duplex scan showing patency of vein cuff anastomosis before discharge*

Discussion

Proximal subclavian artery stenosis may be responsible for symptoms of arm ischaemia, transient ischaemic attacks or the subclavian steal syndrome. Various techniques have been described for the treatment of proximal subclavian artery stenosis, including percutaneous transluminal angioplasty[2], carotid-to-subclavian bypass, subclavian-to-carotid anastomosis[3], and subclavian-to-subclavian bypass. The advantage of subclavian-to-subclavian bypass is that it does not interfere with carotid blood flow[4]. Carotid-to-subclavian bypass has been associated with siphoning of blood from the carotid circulation, causing the carotid steal syndrome[5].

Vein cuffs were originally described and used to facilitate the anastomosis between large stiff PTFE grafts and small distal arteries[6,7]. They are now in frequent use for prosthetic femorodistal grafts. Apart from technical facility there is evidence to suggest that the use of vein cuffs may improve the long-term patency of distal bypass grafts[8]. Experimental models have shown that blood flow is greater through a vein cuff anastomosis than through a standard anastomosis[9].

Subclavian-to-subclavian bypass is a technically demanding operation because of limited exposure and the fragility of the subclavian artery. The use of a vein cuff makes the anastomosis technically easier and safer. As far as we are aware, the use of a vein cuff in subclavian-to-subclavian bypass has not been previously described.

Acknowledgements

We would like to thank Mrs A. Underwood for drawing *Figure 1*.

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References

1. Dickenson PH, Chamberlain J. Vascular disorders of the neck and upper limb. In: Cuschieri A, Giles GR, Moossa AR, eds. *Essential Surgical Practice*. 2nd ed. Bristol: Wright, 1988: 734–51.
2. Tomita S, Doi A, Baba Y *et al*. Two cases of percutaneous transluminal angioplasty for the treatment of subclavian steal syndrome. *No-Shinkei-Geka* 1987; **15**: 561–6.
3. Flanigan DP, Yao JST. Carotid–subclavian bypass. In: Bergan JJ, Yao JST, eds. *Operative Techniques in Vascular Surgery*. New York: Grune and Stratton, 1980: 53–62.
4. Bell PRF, Barrie W. Bypass for subclavian artery occlusion. In: Bell PRF, Barrie W, eds. *Operative Arterial Surgery*. Bristol: Wright, 1981: 64–7.
5. Otis S, Rush M, Thomas M, Dilley R. Carotid steal syndrome following carotid subclavian bypass. *J Vasc Surg* 1984; **1**: 649–52.
6. Seigman F. Use of the venous cuff for graft anastomosis. *Surg Gynecol Obstet* 1979; **148**: 930.
7. Miller JH, Foreman RK, Ferguson L, Faris I. Interposition vein cuff for anastomosis of prosthesis to small artery. *Aust NZ J Surg* 1984; **54**: 283–5.
8. Miller JH. The use of vein cuff and PTFE. In: Greenhalgh RM, ed. *Vascular Surgical Techniques: An Atlas*. London: WB Saunders, 1989: 276–86.
9. Beard JD, Benveniste GL, Miller JH, Horrocks M. Haemodynamics of the interposition vein cuff. *Br J Surg* 1986; **73**: 823–5.

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For debate

Br. J. Surg. 1991, Vol. 78, May, 631

Importance of unilateral absence of the vas deferens

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The vas deferens is a structure which, however carefully identified, isolated and (usually) protected from injury during surgery, is one that is least often sought during routine physical examination. While some reports suggested that congenital absence of the vas deferens was first described in 1926[1], Hunter first described absence of the vas deferens in a cadaver in 1737[2] and the first clinical report of a patient with congenital absence of the vas deferens was actually presented in 1918[3].

The coexistence of genital tract anomalies and renal anomalies was not appreciated until early in this century. Genital defects were noted to be more frequently associated with a solitary kidney than any other type of renal malformation, being found in 70 per cent of females and 21 per cent of males with a solitary kidney[4].

Embryologically the mesonephric (Wolffian) duct forms the ureter, renal pelvis, calyces, collecting tubules, trigone and upper part of the urethra in both males and females. In the male it continues to form the ejaculatory duct, seminal vesicle and the vas deferens.

Congenital absence of the vas deferens therefore highlights the possible existence of anomalies of structures derived from the mesonephric duct. It is estimated that 40 per cent of patients suffering from renal disease have an underlying congenital renal abnormality[5] and that up to 80 per cent of maldeveloped kidneys are prone to affliction by further disease such as infection, obstruction or calculus formation[6]. This makes unilateral congenital absence of the vas deferens a very significant finding indeed. As well as suggesting subfertility or even infertility[7,8], it can be the only clinical pointer to indicate renal tract malformation.

Of patients with unilateral absence of the vas deferens 80 per cent have no ipsilateral kidney. Even when the kidney is present it may be affected by a wide range of anomalies such as ectopia, malrotation, fusion and polycystic disease (12 per cent cases)[8,9]. In a further 10 per cent, contralateral renal anomalies such as ureteric obstruction, and vesicoureteric reflux can exist[9]. These malformations may not in themselves constitute an immediate threat to life, however such patients tolerate genitourinary disease poorly. These findings therefore should cause great concern pre-empting close follow-up in order to prevent potentially permanent and serious sequelae.

With the present popularity of vasectomy, it must be stressed that unilateral absence of the vas deferens should alert the clinician to the possible coexistence of renal anomalies and full urological investigation is mandatory to determine their existence and extent. Patients identified as having unilateral absence of a kidney should be advised to carry a warning card or wear a bracelet or chain describing the condition. Bilateral palpation for the vas deferens is an important part of proper physical examination of all males.

References

1. Charney CW, Gillenwater JY. Congenital absence of the vas deferens. *J Urol* 1965; **93**: 399–401.
2. Hunter J. On the glands called vesiculae seminales. In: Palmer JF, ed. *Complte Works*. London: Longman, Reese, Orm, Brown, Green and Longman, 1737; **4**: 23.
3. Lespinasse V, Clinic of Victor D, Lespinasse MD. Wesley Memorial Hospital, Chicago. *Internat. Clin.* 1918; **1**: 47–53.
4. Fortune CH. The pathological and clinical significance of congenital one-sided kidney defect with the presentation of three new cases of agenesia and one of aplasia. *Ann Intern Med* 1927; **1**: 377–99.
5. Gutierez R. Surgical aspects of renal agenesis with special reference to hypoplastic kidney, renal aplasia and congenital absence of one kidney. *Arch Surg* 1933; **27**: 686–735.
6. Longo VJ. Congenital solitary kidney. *J Urol* 1952; **68**: 63–8.
7. Rubin GP, Taylor I. Congenital absence of the vas deferens. *Br J Surg* 1976; **63**: 464.
8. Dean AM, May RE. Absent vas deferens in association with renal abnormalities. *Br J Urol* 1982; **54**: 298–9.
9. Donohue RE, Fauver HE. Unilateral absence of the vas deferens, a useful clinical sign. *JAMA* 1989; **261**: 1180–2.

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Antabuse® implants: a useful surgical procedure

Sir

It is not surprising that Welch *et al.* reported 'no serious complication resulting from alcohol intake in the presence of an Antabuse® implant occurred'[1], since there is no evidence that the procedure is accompanied by any pharmacologic effects or clinical benefits.

The implantation of disulfiram (Antabuse) tablets was first described by Marie in 1955, in a clinical trial that lacked a control group or any objective index of subsequent alcohol consumption[2]. Surgeons have continued to perform the procedure for more than 30 years, despite the absence of any evidence for its clinical efficacy. However, in a double blind study, Johnsen *et al.* found no difference in the drinking behaviour of alcoholics who had been treated either with implanted disulfiram or implanted placebo[3]. In a subsequent study, Johnsen *et al.* implanted normal volunteers with subcutaneous disulfiram, and challenged them with doses of alcohol; none experienced a significant disulfiram–ethanol reaction[4].

Although the implantation of sterile disulfiram tablets appears to lack any clinical value, the possibility of treating alcoholics with a pharmacologically effective formulation of sustained-release disulfiram remains a worthwhile goal. Preliminary findings with an injectable preparation of sustained-release depot disulfiram suggest that alternative approaches may be effective[5].

Incidentally, Hald and Jacobsen, the pioneers of disulfiram research, were Danish, not Dutch[6].

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1. Welch M, Betts CD and Kiff ES. Antabuse® implants: a useful surgical procedure. *Br J Surg* 1990; **77**: 821.
2. Marie C. A propos d'un nouveau mode de traitement de l'alcoolisme chronique par implantation de disulfure de tétraéthyle-thio-urame. Thèse pour le doctorat en médecine. R. Foulon, Paris 1955.
3. Johnsen J, Stowell A, Bache-Wiig JE, Stensrud T, Ripel A and Morland J. A double-blind placebo controlled study of male alcoholics given a subcutaneous disulfiram implantation. *Br J Addict* 1987; **82**: 607–13.
4. Johnsen J, Stowell A, Stensrud T, Ripel A and Morland J. A double-blind placebo controlled study of healthy volunteers given a subcutaneous disulfiram implantation. *Pharm & Toxicol* 1990; **66**: 227–30.
5. Phillips M. Persistent sensitivity to ethanol following a single dose of parenteral sustained-release disulfiram. *Adv Alcohol Subst Abuse* 1987; 7(1): 51–61.
6. Hald J and Jacobsen E. A drug sensitizing the organism to ethyl alcohol. *Lancet* 1948; **ii**: 1001–4.

Potential hazards of mechanized surgical retractors

Sir

Mr R. J. R. Goodall raises an interesting point in his letter (*Br J Surg* 1990; **77**: 1195) concerning the use of diathermy equipment with table mounted retractors. He has I believe overstated the problem and I hope that the following technical explanation will clarify the situation.

When using grounded or earthed diathermies in the unipolar mode the electrosurgical current flows back to ground via the patient plate electrode. If it cannot do so it will try to follow an alternative pathway such as may be provided by ECG monitoring equipment or the surgeon in contact with the patient and the theatre floor. The possibility of a burn arises if the contact area between this pathway and the patient is small enough to permit a power density of >2·2 W/cm.

Correct use of The Emeltract Mechanised Surgical Retractor in this situation will result in a substantially greater area of contact with the patient and, while it is appreciated that there is a theoretical risk of an accidental burn, Engineering in Medicine Ltd. do not feel that this is of practical significance.

It should be noted that in order for a burn to occur two conditions must be satisfied, namely that there is a fault in the connections between the diathermy unit and the patient and that there is a pathway to earth via the operating table. Modern operating tables are all isolated electrically from earth.

With isolated diathermies used in the unipolar mode the above applies only if the patient plate electrode becomes grounded following disconnection from the patient. The use of diathermy in the bipolar mode does not pose a risk.

As a precaution against inadvertent burns by the routes which have been described the newer diathermy units include a patient earth monitoring circuit which cuts the current off when such a fault arises.

However when using any metal operating instrument in conjunction with diathermy in the unipolar mode it is possible to cause a burn by touching it with the active probe. Once again this relies upon a small area of contact between the instrument and the patient and is a common manoeuvre using small forceps to handle the tissues. To achieve the same result accidentally with a table mounted retractor requires the probe to be left in contact with the metalwork which itself must be in minimal contact with the patient and for the system to be activated simultaneously by depressing the pedal switch. In skilled hands this scenario seems unlikely.

Finally I am pleased to note that Mr Goodall considers retractor systems such as The Emeltract as 'undoubtedly useful' and I hope that he will now feel reassured about their safety.

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Experimental study of starch-induced intraperitoneal adhesions

Sir

McEntee and colleagues (*Br J Surg* 1990; **77**: 1113–4) have shown that the intraperitoneal injection of starch does not result in the formation of peritoneal adhesions unless a laparotomy is also performed. Similarly intraperitoneal instillation of fresh or clotted blood does not induce adhesions in the absence of intestinal serosal injury[1].

We have carried out a series of experiments on adhesion formation using a rat model and have also found that limited contamination of the parietal peritoneum with faecal material does not cause significant adhesions. Our studies support the work of Professor Ellis who observed that abrasion of the parietal peritoneum alone did not produce adhesions[2]. If however the traumatized peritoneum is contaminated with faecal material (as in our first group of rats) then very dense adhesions result. The probable explanation is that peritoneal injury diminishes tissue plasminogen activation[3] and the presence of foreign material in the damaged area may thus cause adhesion formation.

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1. Nissell H, Larsson B. Role of blood and fibrinogen in the development of intraperitoneal adhesions in rats. *Fertil Steril* 1978; **30**: 470–3.
2. Ellis H. The aetiology of postoperative abdominal adhesions. *Br J Surg* 1962; **50**: 10–16.
3. Raftery AT. Effect of peritoneal trauma upon peritoneal fibrinolytic activity and intraperitoneal adhesion formation. An experimental study in the rat. *Eur Surg Res* 1981; **13**: 397–401.

Development and reversibility of T lymphocyte dysfunction in experimental obstructive jaundice

Sir

We read with interest the article by Thompson *et al.* (*Br J Surg* 1990; **77**: 1229–32) in which they showed a T lymphocyte dysfunction in obstructive jaundice and reversibility after internal biliary drainage. This is not surprising because comparable data were reported previously[1]. It is however interesting that there is no significant increase of T lymphocyte function after external biliary drainage. The authors therefore suggest that external biliary drainage is not as effective as internal drainage. This is in accordance with our previous study in which we found in rats with obstructive jaundice no reduction of mortality after preoperative external biliary drainage but significant reduction of mortality after internal biliary drainage[2]. It is therefore remarkable that Thompson *et al.* reported at the same time another study in which they did not show any difference in mortality after external or internal biliary drainage[3]. Here the authors stated that 'restoration of bile flow (internal drainage) cannot be used as an explanation for the failure of external biliary drainage'. This seems to be in contrast with the difference of reversibilty of T lymphocyte dysfunction after internal or external biliary drainage reported in the present study. Furthermore the author stated that the cause of T lymphocyte depression is unknown.

We recently performed a study with germ-free (endotoxin free) animals, in which we showed that T lymphocyte dysfunction in obstructive jaundice is caused by endotoxin[4]. Bile duct ligation in conventional rats resulted in a suppression of cellular immunity similar to the suppression found in conventional non-jaundiced rats treated with a chronic low dose of endotoxins. However after bile duct ligation in germ-free rats cellular immunity was not impaired. This indicates that endotoxins play the crucial role in the suppression of cellular immunity in obstructive jaundice despite the fact that measurement of the serum endotoxin levels remains controversial[4,5]. The nutritional status could be excluded as another factor for the suppression of cellular immunity[4,6]. Knowing that T lymphocyte dysfunction is caused by endotoxins means that normalizaton of T lymphocyte after external biliary drainage can hardly be expected.

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1. Roughneen PT, Gouma DJ, Kulkarni D, Fanslow WF, Rowlands BJ. Impaired specific cell-mediated immunity in experimental biliary obstruction and its reversibility by internal biliary drainage. *J Surg Res* 1986; **41**: 113–25.
2. Gouma DJ, Coelho JCU, Schlegel JF, Li YF, Moody FG. The effect of preoperative internal and external biliary drainage on mortality of jaundiced rats. *Arch Surg* 1987; **122**: 731–4.
3. Diamond Th, Dolan SMB, Thompson RLE, Rowlands BJ. Development and reversal of endotoxemia and endotoxin related death in obstructive jaundice. *Surgery* 1990; **108**: 370–5.
4. Greve JW, Gouma DJ, Soeters PB, Buurman WA. Suppression of cellular immunity in obstructive jaundice is caused by endotoxins. *Gastroenterology* 1990; **98**: 478–85.
5. Gouma DJ, Coelho JCU, Fisher JD, Schlegel JF, Li YF, Moody FG. Endotoxemia after relief of biliary obstruction by internal and external drainage in rats. *Am J Surg* 1986 **151**: 476–9.
6. Gouma DJ, Roughneen PT, Kumar S, Moody FG, Rowlands BJ. Changes in nutritional status associated with obstructive jaundice and biliary drainage in rats. *Am J Clin Nutr* 1986; **44**: 362–9.

Authors' reply

Sir

Gouma *et al.* recently published an excellent study supporting endotoxin as the cause of T lymphocyte depression in obstructive jaundice[1]. We agree that endotoxin is probably the major contributory factor, but others such as bile acids, bilirubin and various cytokines may be important.

We are surprised they question the similar mortality rate following external and internal biliary drainage in our previous study, especially as we showed similar reversal of endotoxaemia by both drainage methods[2]. This is entirely consistent with their own hypothesis of the primary importance of endotoxaemia.

Their confusion may relate to our use of a choledochovesical fistula as a sterile model for external biliary drainage[3], whereas their model of drainage to the skin surface may introduce an additional source of bacterial infection and endotoxaemia. This is a possible explanation for the higher mortality in their externally drained animals[4].

We would not expect normalization of T lymphocyte function in their model but we have recently shown that in our endotoxin free model T lymphocyte function returns to control values after 3 weeks drainage[5].

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1. Greve JW, Gouma DJ, Soeters PB, Buurman WA. Suppression of cellular immunity in obstructive jaundice is caused by endotoxins. *Gastroenterology* 1990; **98**: 478–85.
2. Diamond T, Dolan SMB, Thompson RLE, Rowlands BJ. Development and reversal of endotoxemia and endotoxin-related death in obstructive jaundice. *Surgery* 1990; **108**: 370–5.
3. Diamond T, Rowlands BJ. Choledochovesical fistula: a model for sterile 'external' biliary drainage. *Surg Res Commun* 1990; **8**: 131–8.
4. Gouma DJ, Coelho JCU, Schlegel JF, Li YF, Moody FG. The effect of preoperative internal and external biliary drainage on mortality of jaundiced rats. *Arch Surg* 1987; **122**: 731–4.
5. McCrory DC, Hoper M, Crockard A, Halliday I, Rowlands BJ. The reversibility of depressed immunity in cholestasis and the role of T cell subsets. *Br J Surg* (SRS Abstract, in press)

Choice of emergency operative procedure for bleeding duodenal ulcer

Sir

I wish to take issue with Drs Hunt and McIntyre choice of emergency operative procedure for bleeding duodenal ulcer (*Br J Surg* 1990; **77**: 1004–6).

The authors suggested that Billroth II partial gastrectomy is an acceptable surgical alternative, particularly in case of giant ulcers. In their experience truncal vagotomy and pyloroplasty (TV + P) and partial gastrectomy resulted in similar mortality rates. Their results could have been more persuasive had they demonstrated that the patients undergoing both procedures belonged to similar risk groups. We have previously shown that in high-risk patients (with APACHE II score greater than 10) undergoing operation for bleeding peptic ulcers, lesser procedures (e.g. VP + P) may carry lower mortality rates than gastric resection[1]. Indeed studies comparing different emergency management modalities in the surgical patients do not contribute much to our knowledge if objective measurements of the severity of acute illness (e.g. APACHE II) are not included.

Interestingly, 17 out of their 101 patients re-bled after TV + P and reoperation was necessary in seven of them. Only one of the eight patients who bled after gastrectomy required reoperation. In our experience major postoperative haemorrhage was as common following gastric resection as after nonresective procedures[2]. Meticulous underrunning of the ulcer bed (in a few directions) could have probably decreased their excessively high rate of rebleeding.

I find it also hard to agree with the authors' dictum that if the duodenum is grossly deformed (e.g. giant ulcer) 'then resection and closure of the duodenum is usually necessary'. This is a dangerous recommendation. The best way to prevent the formation of a difficult duodenal stump is not to create one at all! If local tissue conditions preclude easy fashioning of a pyloroplasty, TV and gastroenterostomy or highly selective vagotomy with or without gastroenterostomy are excellent alternatives. Furthermore, even in the extremely rare case when gastrectomy is needed, the closure of a 'difficult' duodenal stump is seldom necessary. Instead, when the duodenal bulb is grossly deformed or a giant ulcer is present Billroth I anastomosis, joining the stomach to the healthy duodenum beyond the ulcer crater, is easily and safely accomplished[3].

I suggest that the correct choice of operative procedure for bleeding duodenal ulcer is as follows: high risk patients (APACHE II greater than 10) should be treated with TV + P and careful underrunning of the bleeding point or ulcer bed. If a giant ulcer or severe scarring are present gastroenterostomy is preferable to pyloroplasty. Low risk patients (APACHE II lower than 11) can be safely managed with a direct attack on the bleeding point followed by a highly selective vagotomy. Gastrectomy is rarely, if ever, indicated. I believe that the above policy may allow the uncomplicated survival of more patients as well as more stomachs . . .

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1. Schein M, Gecelter G. APACHE II score in massive upper gastrointestinal haemorrhage from peptic ulcer: prognostic value and potential clinical applications. *Br J Surg* 1989; **76**: 733–6.
2. Schein M, Decker GAG. Five hundred operations for peptic ulcer disease at J. G. Strijdom Hospital, 1980–1987. *S Afr J Surg* 1989; **27**: 161–7.
3. Schein M, Gecelter G. Gastroduodenostomy for the 'difficult' duodenum. *S Afr J Surg* 1990; **28**: 16–17.

Authors' reply

Sir

We presume that Mr Schein failed to see that a comparison of risk was made in our paper. Patients in the two main surgical groups were assessed as similar according to the American Association of Anaesthetists scale. This finding supports the contention that partial gastrectomy is an acceptable alternative to vagotomy and pyloroplasty in certain cases with bleeding duodenal ulcer.

P. S. Hunt
R. McIntyre

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Irreducible inguinal hernia in children below two years of age

Sir

This paper by Davies *et al.* (*Br J Surg* 1990; **77**: 1291–2) is an important reminder that, among children, irreducibility of an inguinal hernia is largely a problem of the first year of life, with 81 per cent of the 85 infants being less than 6 months of age. The authors rightly emphasize that in 40 per cent of their patients irreducibility could have been avoided if the pre-existing hernia had been promptly treated. Among the 60 per cent who present only when the hernia is irreducible, the majority will reduce with sedation and posture. Those who do not respond are younger (mean 12 weeks old) than those who do (mean 19 weeks of age), and this is not the only problem which these sick babies present to both surgeon and anaesthetist.

Paediatric surgeons with the experience of Puri, Guiney and O'Donnell[1] make this very clear when they state that 'emergency herniotomy for infantile incarcerated inguinal hernia is one of the most difficult operations in the paediatric surgeon's repertoire'. These difficulties are certainly not lessened if the oedematous friable tissues are approched through the inguinal canal, and we are convinced of the value of an extraperitoneal approach[2,3] which allows easy identification and isolation of the spermatic vessels and vas, and controlled reduction of the hernial contents through the neck of the sac above the internal ring. Although late perforation of ischaemic bowel is rarely described nowadays, both Clatworthy[4] and Smith[5] describe fatal cases in which discoloured bowel was mistakenly considered to be viable and returned to the abdomen. Both assessment of bruising and ischaemia, and the occasional resection, is made easier when the doubtful bowel can be brought out through an abdominal incision.

The anaesthetist needs to be as skilled in the care of these infants as the surgeon[6]. Many of these young babies were born preterm, and with the mean duration of irreducibility of 36 hours, many will be appreciably dehydrated. Three of the 14 babies suffered 'potentially serious' respiratory complications.

We believe that the facts provided in this and in other papers present a strong case for recommending that, for the small number of babies who require emergency surgery, this should be performed in a unit in which an experienced paediatric anaesthetist and surgery are available.

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1. Puri P, Guiney EJ, O'Donnell B. Inguinal hernia in infants: the fate of the testis following incarceration. *J Paed Surg* 1984; **19**: 44–6.
2. Fowler R. Preperitoneal repair of inguinal hernias in infancy and childhood. *Aust Paed J* 1973; **9**: 85–9.
3. Jones PF, Towns GM. An abdominal extraperitoneal approach for the incarcerated inguinal hernia of infancy. *Br J Surg* 1983; **70**: 719–20.
4. Clatworthy HW, Thompson AG. Incarcerated and strangulated inguinal hernia in infants: a preventable risk. *JAMA* 1954; **154**: 123–6.
5. Smith I. Irreducible inguinal herniae in children. *Br J Surg* 1954; **42**: 271–4.
6. Campling EA, Devlin HB, Lunn JN. Report of the National Confidential Enquiry into Perioperative Deaths 1989. June 1990.

Intersecting staple lines and blood flow in oesophagojejunal anastomoses

Sir

I have read the article on intersecting staple lines and blood flow in oesophagojejunal anastomoses by Zilling, Walther, and Ranstam (*Br J Surg* 1990; **77**: 1735–8) with considerable interest. One has no difficulty accepting their numerical results. However, one has some difficulty in accepting their conclusions. Their data, they say, 'confirm that intersecting staple lines in oesophageal anastomoses do not reduce mean anastomotic blood flow to a dangerous level'. Unfortunately, the only estimate of 'dangerous level' I see in the paper is a passing reference to a 30 per cent reduction being tolerated without mucosal infarction. Unfortunately, as perfusion falls, the ability to sustain repair and resistance to infection falls far before infarction occurs[1]. The level of reduction tolerated by resistance to infection would seem to me to be the dangeous level, and the authors do not define it.

Furthermore, blood circulation in and around the oesophagus varies with vascular anatomy. One of their 22 animals had a severe restriction in blood flow, presumably due to a circulation 'anomaly'. Presumably 1 of every 22 humans will also have anatomical variants, and one in 22 cannot be ignored. The question is not whether any given method can be relied upon to give a high statistical probability of perfusion which is adequate to prevent infarction. The question really is how can one define methods which are safe in as close to 100 per cent of patients as possible.

These results are interesting and valuable, but they do not necessarily define intersecting staple lines as the best, or even necessarily as an acceptable technique.

T. K. Hunt

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1. Jonsson K, Hunt TK, Mathes SJ. Oxygen as an isolated variable influences resistance to infection. *Ann Surg* 1988; **208**: 783–7.

Endoscopic transthoracic electrocautery of the sympathetic chain for palmar and axillary hyperhidrosis

Sir

In their recent paper (*Br J Surg* 1990; **77**: 1046–9) Byrne *et al.* perform a valuable service for they imply that this form of sympathectomy has now established itself as the operation of choice, relegating anterior and transaxillary sympathectomies to historical interest only. In the second paragraph of their discussion they rightly point to differences between the method they describe and that of Kux (and Wittmoser), who in the fifties had thought of destroying the sympathetic chain by diathermy. The authors go on to say that they can justify passing a diathermy probe through an incision separate to that of the laparoscope because allegedly younger patients have narrower intercostal spaces and a finer laparoscope would cause less postoperative pain. However, the mean age of their patients was 24·3 years and one would assume that they were therefore fully grown.

Their technique is to all intents and purposes that described independently in this country[1], with one practical, and to those who wish to adopt this technique, important difference.

For an operation to establish itself its technique must be as straightforward as possible. It is regrettable therefore that they have not used or recommended readily available laparoscopes which provide their own diathermy channel, reduce the incisions to one, and provide much easier handling. Their *Figure 1* well illustrates the awkwardness of employing two incisions. It is evident from it that the tip of the diathermy is quite out of line with the laparoscopic objective, and extra three-dimensional manipulation will be necessary to bring the diathermy into view. Furthermore it is an added advantage for the diathermy to impinge on the heads of the ribs (not the necks) at right angles rather than obliquely. Familarity with minimally invasive surgery employing two separate instruments is not yet widespread; when this is unavoidable it is justified. However, that is not the case with transthoracic electrocoagulation.

F. Weale

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1. Weale FE. Upper thoracic sympathectomy by transthoracic electrocoagulation. *Br J Surg* 1980; **67**: 71–2.

Quote ... Unquote!

Sir

I do not suppose high literary standards are of enormous consequence for leader writers in *The British Journal of Surgery* but no one likes to be misquoted and both the leaders in your January issue contain unnecessary solecisms.

Mr Gough may like to know that it was not Bernard Shaw but one of the playwright's characters in 'The Doctor's Dilemma' who said "Stimulate the phagocytes" and he used the plural not the singular. Shaw got his understanding of the subject from Almoth Wright at St. Mary's with whom he was acquainted. Mr Heald's quotation from 'The Memoirs of Sherlock Holmes' is so far away from the original text as to constitute a literary crime against Conan Doyle. He cannot have checked either the original or, what is easier for most of us, the Oxford Dictionary of Quotations in which the 'curious' (not singular) incident is recorded correctly.

H. Dudley

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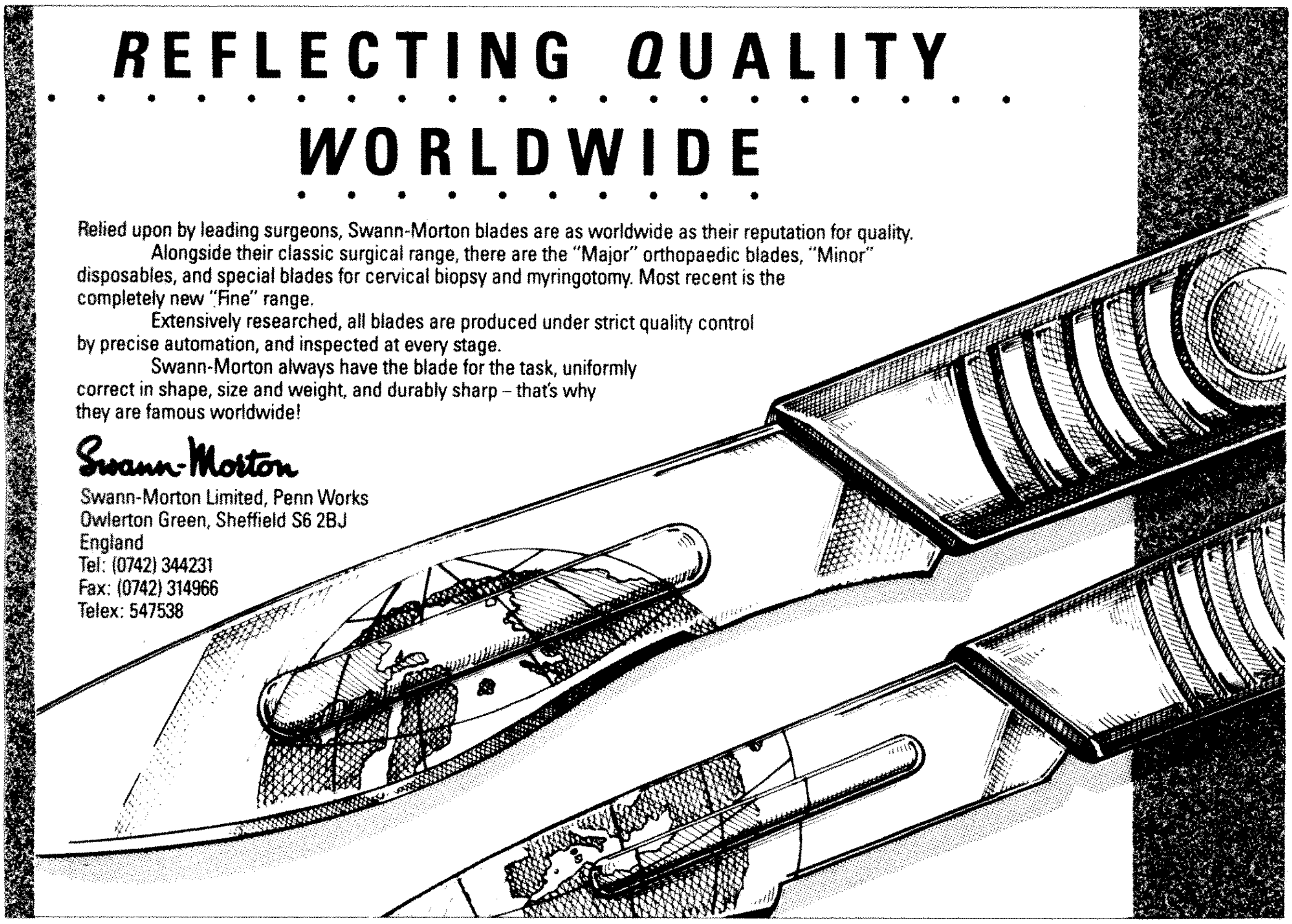

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Book reviews

Tutorials for Junior Students of Surgery

G. L. Hill and A. G. Hill. 215 × 135 mm. Pp. 124. 1990. Edinburgh, Churchill-Livingstone. £6.95 softback.

This is a superb little book for medical students starting surgery and should also appeal to nurses on surgical wards.

The tutorials cover diagnosis and management of most common surgical conditions and do so in a readable, explicit, and practical way. Important points are emphasized by clear statement and/or italics. There are useful lists for the beginner – for example the causes of haematemesis and melaena (with percentages) and 'Stomach operations – glossary of terms'.

The succinct and didactic style means that methods of diagnosis and treatment are somewhat individualistic in areas where practice varies considerably. The occasional point is sufficiently out of tune to raise hackles, such as the description of haemorrhoids as 'varicosed veins'. Some detail (for example types of intravenous fluids used in New Zealand) vary a little from British practice but these details are overshadowed by the sound practical advice on general principles.

The first three chapters give particular strength to the book. They cover preparation of the patient for surgery, peri-operative care, and metabolic care thoroughly, simply, and pragmatically.

I am about to put this book on the ward bookshelf for the nurses, and first year medical students will receive Draconian instructions to digest the early chapters within hours of their arrival.

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Vascular Surgery: A Comprehensive Review (3rd edition)

W. S. Moore (ed.) 280 × 210 mm. Pp. 767. Illustrated. 1991. Philadelphia, W.B. Saunders. £76.00.

Continuing rapid progress in our understanding of peripheral vascular disease and, particularly, of its management, requires the editors of textbooks on the subject to revise their works frequently. This 3rd edition of Wesley S. Moores's 'Vascular Surgery' is published 4 years after its predecessor. The book is a compilation of 40 chapters from 62 North American authors of excellent vascular surgical credentials, lending great weight to the text. With such a provenance some transatlantic bias is inevitable, for instance in the section dealing with the management of extracranial cerebrovascular disease, but its influence is not great and should not detract from the non-American reader's enjoyment.

This is one of the major textbooks of vascular surgery; it is both authoritative and up to date, and it is good to see new chapters on 'Anatomy, Physiology and Pharmacology of the Vascular Wall', on 'The Natural History and Nonoperative Treatment of Chronic Lower Extremity Ischaemia' and on 'Endovascular Surgery'. This last topic will, I am sure, receive increasing attention in future years.

Despite the wide range of activity covered, the book is somewhat idiosyncratic in its spread of subject matter; its claim to be a 'comprehensive' review of vascular surgery is odd as it deals to any significant extent only with arterial disease. Varicose veins are relegated to only eight pages, even less than lymphatic disease which occupies a rather paltry 11 pages.

The volume was conceived as an aid for postgraduate surgical students preparing for board certification in general vascular surgery and at the end of each chapter there is a list of questions for the reader's self assessment. While it is perhaps less 'operative' than many of the competing textbooks, it certainly gives a wide view of modern arterial surgery. In what is a competitive area of surgical publication this readable volume may well appeal to those in higher surgical training.

J. Murie

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Surgical Roots and Branches

Sir Reginald Murley. 220 × 140 mm. Pp. 326. The Memoir Club. £14.95 hardback, and

Travels of a Surgeon

Arthur Eyre Brook. 240 × 160 mm. Pp. 189. Bristol, White Tree Books. £12.95 hardback

Memoirs can be dangerous, both for the author and his contemporaries, and for the book reviewer. Autobiography relies on selective memory, personal interpretation and well judged legal opinion if libel is to be avoided. Sir Reginald Murley is well known to British surgeons, and to numerous others with interests in the NHS! He is a man of stout opinion who is never frightened to speak out. This memoir conveys these sterling qualities admirably. When you meet him, Sir Reginald instantly starts giving you the Murley message, you cannot but listen, he drives his points home and isn't frightened of repetition to strengthen his case. All the Murley personality is vividly conveyed in this autobiography.

The text of his autobiograph, **Surgical Root and Branches**, falls into three parts.

The pre-consultant epoch, which is written with detail and zest, was very interesting to me; how childhood and education influence maturity is fascinating. The influence of war service and the extensive professional network it built up was for long the consensus of the National Health Service. Indeed the current NHS reforms are the product of the decay of that wartime cameraderie and consensus.

Then the consultant epoch, Murley the smart, hard-working provincial surgeon. Again a topic close to my own experience. Clearly Murley had a tough time sorting out an adequate surgical service for St. Albans. Although the 60s are said to be the high spot of the NHS, that view is challenged by the experience recounted here.

And then we come to the latter third of the book, Murley Triumphant, he's made it to President of the Royal College of Surgeons. But suddenly the book implodes. You can speculate where prudence has prevailed. This is certainly a tragedy because Murley was a decisive, and not uncontroversial, leader of our profession. Hopefully a fuller script and footnotes are safely under lock and key to be revealed later!

I enjoyed part one enormously, part two was good but Murley's experience is little different from that of many provincial consultants though he deserves full marks for chronicling these times so well. What is missing is a blow-by-blow account of the internecine struggles both between College Presidents and between our medical and our political leaders. Hopefully there will be a further instalment.

Arthur Eyre-Brook is an endearing character and this slim volume speaks so much about him. This book is no mere travelogue but a gentle apologia for a life spent in the service of others. Eyre-Brook is a dedicated orthopaedic surgeon who has sought no honour other than to care for patients well. After a career as a consultant orthopaedic surgeon in Bristol, during which he was president of the British Orthopaedic Association, Eyre-Brook embarked on a second career as a visiting orthopaedic surgeon to many poorer nations. Although this book describes an initial visit to the USA as a young man, the bulk of the book is about the Third World, Africa, South America, the Near and the Far East. Anyone who has visited hospitals in the third world will find much of interest. The descriptions of the political set-up and the problems of medicine will readily strike chords. Like Eyre-Brook my sympathy goes to the patients who suffer under curious regimes.

I have really enjoyed reading this book. It describes the idealist medicine which attracted me as a young man. Like many young men grown old I have become sceptical of the politicians who today dictate much of the practice of medicine. We doctors must preserve our ethics and the idealism that inspires good doctoring. Eyre-Brook reticently describes how he achieved these ideals. A very encouraging testament to a life well spent.

H. Brendan Devlin

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Notices and announcements

15–18 May 1991
82nd Annual Meeting of the American Association for Cancer Research
Houston, Texas, USA
Information: American Association for Cancer Research, Public Ledger Building, Suite 816, Sixth and Chestnut Streets, Philadelphia, PA 19106, USA

17 May 1991
British Association for Endocrine Surgeons
Cambridge, UK
Information: Mr A. W. Goode, Surgical Unit, 4th Floor Alex Wing, The Royal London, London E1 1BB, UK

20–22 May 1991
Trauma 91
Witwatersrand, South Africa
Information: Gwen Watkins, Kennedy, Watkins & Associates, 27 Landau Terrace, Richmond 2092, South Africa

20–24 May 1991
Pacific Association of Paediatric Surgeons 24th Annual Meeting
Hong Kong
Information: Secretariat, PAPS Hong Kong, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

24–25 May 1991
Surgical Infection Society – Europe, 4th Annual Meeting
Athens, Greece
Information: Triaena Congress, 22–24 Harilaou Trikoupi Street, GR-106 79 Athens, Greece

24–25 May 1991
MedTech '91
Trondheim, Norway
Information: Laser-Medizin-Zentrum GmbH, Koordinations Buro MedTech, Krahmerstr. 6–10, 1000 Berlin 45, Germany

30 May–1 June 1991
4th International Symposium on the Biology, Immunology and Surgery of the Greater Omentum
The Netherlands
Information: Secretariat, 4th International Omentum Symposium, Mrs W. J. Buys – Utrecht Cancer Research Centre, Servaasbolwerk 14, 3512 NK Utrecht, The Netherlands

June 1991
33rd Annual Meeting of the International College of Angiology
Singapore
Information: International College of Angiology, 1044 Northern Blvd., Ste 103, Roslyn, New York 11576, USA

2–14 June 1991
Methods of Immunologic Research and Diagnosis
Buffalo, New York, USA
Information: James F. Mohn, Director, The Ernest Witebsky Center for Immunology, 272 Sherman Hall, Buffalo, New York 14214, USA

6–8 June 1991
5th European Congress of the Society for Surgery of the Shoulder and the Elbow
Wurzburg, FRG
Information: Prof. Dr. med. J. Eulert, Orthpadische Universitatsklinik, Konig-Ludwig-Haus, Brettreichstr. 11, 8700 Wursburg, FRG

6–10 June 1991
American College of Cryosurgery 12th Annual Scientific Meeting
La Jolla, California, USA
Information: American College of Cryosurgery, Attn. Michael Thompson, PO Box 3116, Evanston, IL 60204-3116, USA

9–12 June 1991
Fifth International Conference on Malignant Lymphoma
Lugano, Switzerland
Information: F. Cavalli, Division of Oncology, Ospedale San Giovanni, 6500 Bellinzona, Switzerland

19–22 June 1991
73rd Annual Meeting of The Endocrine Society
Washington, D.C., USA
Information: The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814, USA

4–5 July 1991
74th Meeting of the Surgical Research Society
Lancaster, UK
Information: Professor J. R. Farndon, Department of Surgery, University of Bristol, Bristol BS2 8HW, UK

11–13 July 1991
XVIth International Update on Liver Disease
London, UK
Information: Professor Neil McIntyre, Academic Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG, UK

12–13 July 1991
Hong Kong Surgical Forum
Hong Kong
Information: Vera Fung, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

14–16 July 1991
Techniques in Pulmonary and Oesophageal Surgery
Liverpool, UK
Information: Mr R. J. Donnell, Cardiothoracic Centre, Broadgreen Hospital, Thomas Drive, Liverpool L14 3LB, UK

25–31 August 1991
International Surgical Week
Stockholm, Sweden
Information: Scientific Secretariat, 155, Hauptstrasse 63, PO Box 411, CH-4153, Reinach BL1, Switzerland

1–6 September 1991
6th World Congress in Ultrasound
Copenhagen, Denmark
Information: Spadville Congress Service, Sommervaj 3, DK-3100 Hornbaek, Denmark

4–6 September 1991
Oxford 1991, Graft Infiltration Meeting
Oxford, UK
Information: Catherine Hughes, Nuffield Department of Surgery, John Radcliffe Hospital, Headington, Oxford OX3 9DU, UK

4–6 September 1991
1st European Conference on Advances in Wound Management
Cardiff, UK
Information: Christine Jones, Macmillan Conferences, 4 Little Essex Street, London WC2R 3LF, UK

20–23 September 1991
60th Annual Meeting of the Royal College of Physicians and Surgeons of Canada
Quebec City, Quebec, Canada
Information: Anna Lee Chabot, The Royal College of Physicians and Surgeons of Canada, 74 Stanley, Ottawa, Canada K1M 1P4

7–10 October 1991
5th Congress of the European Society for Organ Transplantation
Maastricht, The Netherlands
Information: 5th ESOT Congress, Conference Agency Limburg, University Hospital Limburg, PO Box 1918, 6201 BX Maastricht, The Netherlands

7–9 November 1991
3rd Combined Meeting of the Nederlandse Vereniging voor Thoraxchirurgie and the Deutsche Gesellschaft für Thorax-, Herz- und Gefässchirurgie
Maastricht, The Netherlands
Information: Organizing Secretariat, Conference Agency Limburg, University Hospital Maastricht, PO Box 1918, 6201 BX Maastricht, The Netherlands

7–10 November 1991
XVII European Society for Medical Oncology Conference
Lyon, France
Information: Michel Clavel, MD, XVII Congress ESMO, CLB, 28, rue Laennec, 69373 Lyon Cedex 08, France

17–23 November 1991
Surgery of the Pancreas, Liver and Biliary System
Edinburgh, UK
Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

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The Association for Surgical Education

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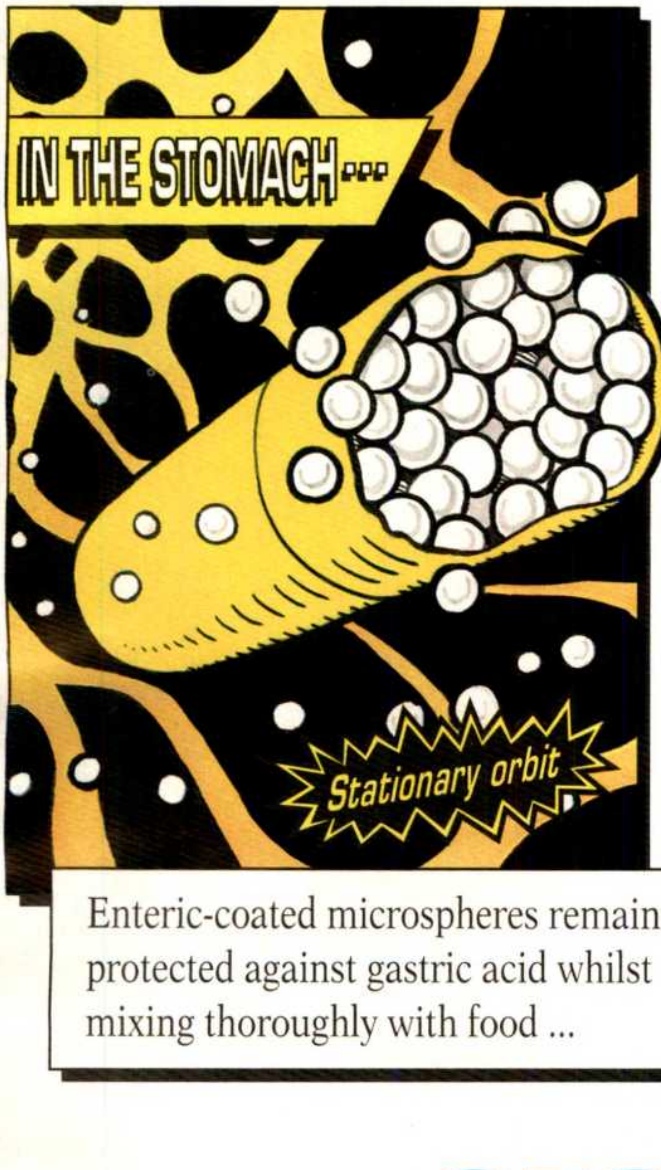

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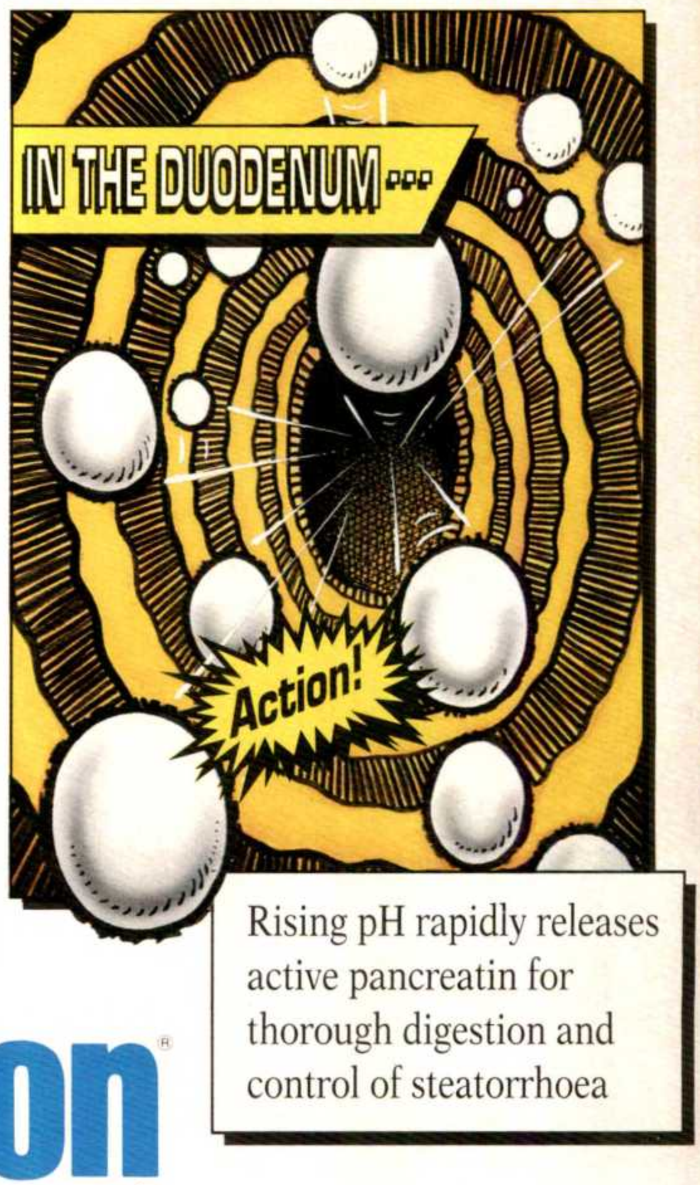
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Presentation: Brown-yellow capsules containing enteric coated granules of pancreatin equivalent to: 9,000 BP units of amylase; 8,000 BP units of lipase; 210 BP units of protease. Available in packs of 100. Basic NHS price £13.33.

Indication: Pancreatic exocrine insufficiency.

Dosage and administration: Adults and children: Initially one or two capsules with meals, then adjust according to response. The capsules can be swallowed whole, or for ease of administration they may be opened and the granules taken with fluid or soft food, but without chewing. If the granules are mixed with food, it is important that they are taken immediately, or otherwise dissolution of the enteric coating may result.

Contra-indications, Warnings, etc.: Contra-indications: Substitution with pancreatic enzymes is contra-indicated in the early stages of acute pancreatitis.

Warnings: Use in pregnancy; there is inadequate evidence of safety in use during pregnancy.

The product is of porcine origin.

Rarely cases of hyper-uricosuria and hyper-uricaemia have been reported with high doses of pancreatin. Overdosage could precipitate meconium ileus equivalent.

Perianal irritation could occur, and, rarely, inflammation when large doses are used.

Product Licence Number: 5727/0001.

Name and address of Licence Holder: Kali Chemie Pharma GmbH, Postfach 220, D-3000, Hannover 1, West Germany.

References

1. Stead RJ et al. *Thorax* 1987;**42**:533-537. 2. Beverley DW et al. *Arch Dis Child* 1987;**62**:564-568.

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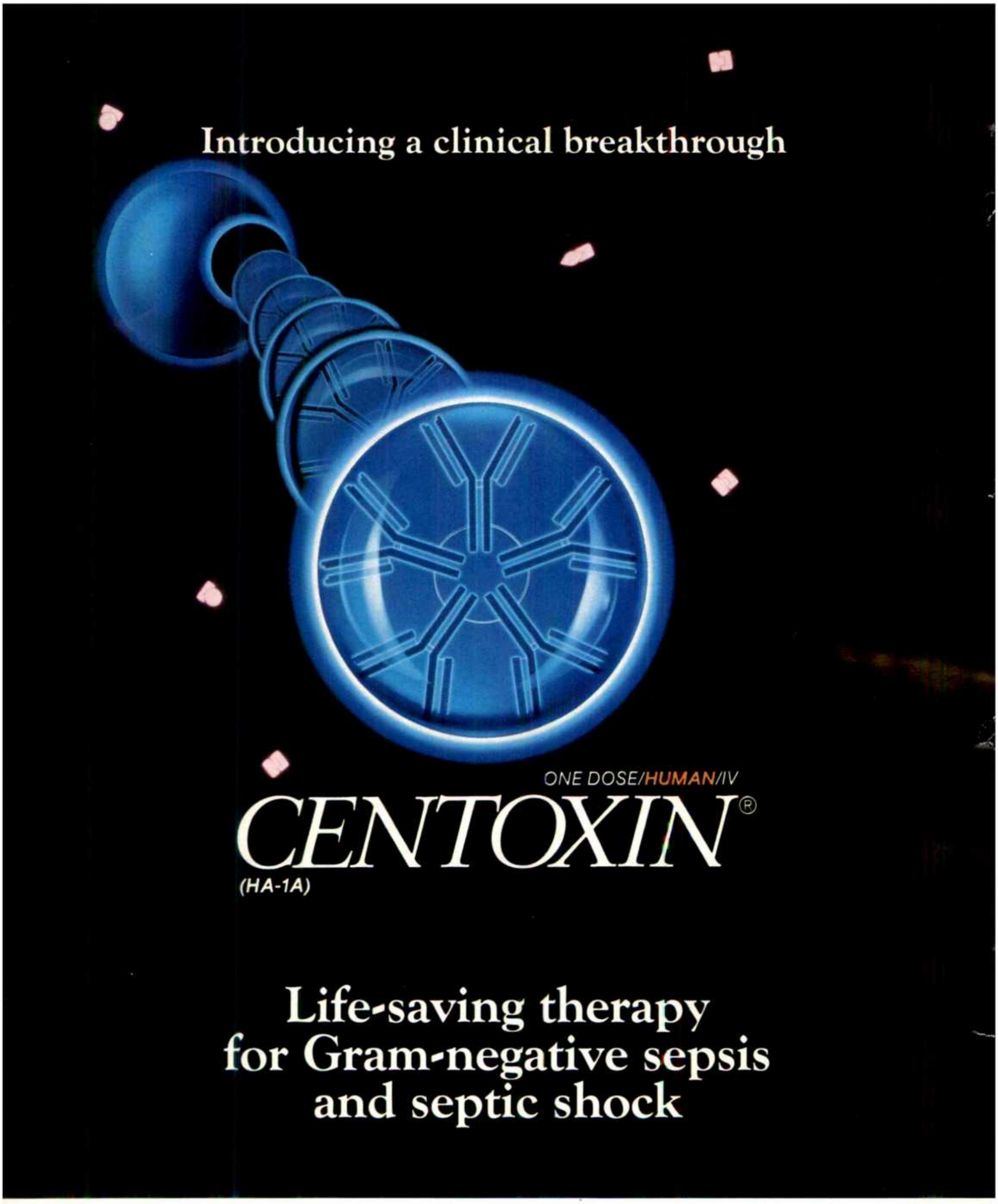
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Life-saving therapy for Gram-negative sepsis and septic shock

ABBREVIATED PRESCRIBING INFORMATION

PRESENTATION Centoxin is a solution for intravenous infusion after dilution with normal saline. Each vial contains: HA-1A 100 mg/20 ml

USES Centoxin is indicated for the treatment of patients with the sepsis syndrome and a presumptive diagnosis of Gram-negative bacteraemia, especially those with septic shock. Centoxin therapy should be given in hospital, along with the appropriate antibiotics and supportive therapy, as soon as Gram-negative sepsis is clinically suspected. Centoxin should be given once and is not intended for repeated use.

DOSAGE AND ADMINISTRATION The recommended dose of Centoxin is a single 100 mg intravenous infusion. Centoxin should be administered intravenously over a period of 15 to 30 minutes in a total volume of 70 mL after dilution with normal saline for injection. In patients studied to date, it has not been necessary to adjust the dosage for renal or hepatic function.

CONTRA-INDICATIONS, WARNINGS ETC. Contra-indications Centoxin should not be used in patients whose primary injury involves burns, since no studies have been done in those patients. Centoxin should not be used in patients with known hypersensitivity to murine proteins. Centoxin should not be used in patients with previous exposure to HA-1A. **Undesirable Effects** No serious or life-threatening adverse reactions attributable to Centoxin were reported among the more than 300 patients who received the product in clinical trials, including more than 45 patients who received 200 or 300 mg of HA-1A as a single dose. Transient flushing, localized urticaria and hypotension have been reported rarely (<1%) in patients receiving Centoxin. Human antibodies against Centoxin have not been detected. **Special Precautions** *In vitro* and *in vivo* mutagenicity studies have not demonstrated any mutagenic effect. Studies have not been performed to evaluate the carcinogenic potential or effects on fertility in male or female animals. The use of Centoxin in children has not been extensively studied. Centoxin has been administered to a small group of children (ages 10 months to 13 years), the majority of whom had fulminant meningococcaemia with shock and purpura. The dose administered was up to 6 mg/kg to a maximal dose of 100 mg. Centoxin was well tolerated by all patients. The efficacy of Centoxin in adults and children with meningococcal septicaemia has not been established and therefore the use of Centoxin in meningococcal septicaemia cannot be recommended. Centoxin contains a murine J chain, which suggests that anti-HA-1A

CENTOXIN: The first human monoclonal antibody specifically directed against endotoxin

Centoxin (HA-1A) is a human monoclonal IgM antibody targeted against endotoxin – the substance largely responsible for multiple organ failure and death associated with Gram-negative sepsis and septic shock. Centoxin neutralizes the lethal effects of endotoxin and helps save the lives of septic patients.

Early and sustained reductions in mortality in Gram-negative sepsis and septic shock

In a multicentre, double-blind, placebo-controlled trial, Centoxin was administered to septic patients with presumptive Gram-negative bacteraemia, including those with septic shock. Clinical results demonstrate significant early and sustained reductions in mortality in septic patients with Gram-negative bacteraemia, especially those with septic shock.[1]

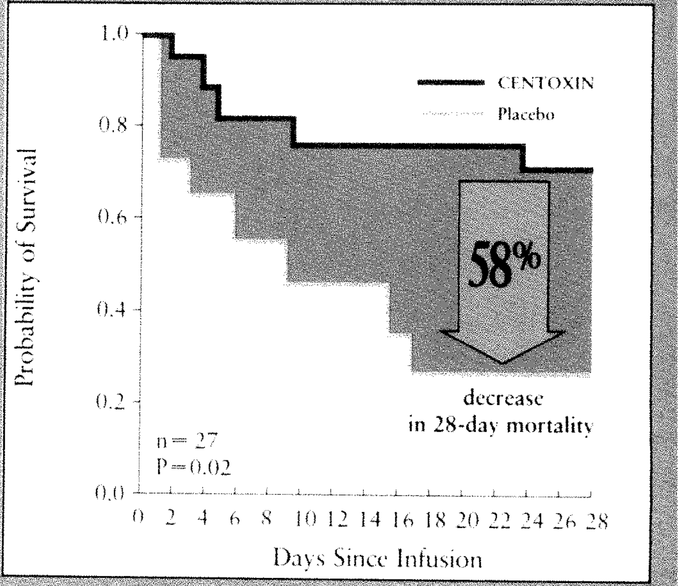
Reduction in 28-day mortality[1]

	Mortality			
Population	Placebo*	Centoxin	% Reduction	*P* Value
Gram-Negative Bacteraemia (N=200)	49% (45/92)	30% (32/105)	39%	0.014
Gram-Negative Bacteraemia with Shock (N=102)	57% (27/47)	33% (18/54)	42%	0.017

*Three placebo-group patients (one with shock) were discharged from the hospital and lost to follow-up before day 28.

58% decrease in mortality in endotoxaemic patients[2]

Centoxin decreased mortality in endotoxaemic patients – patients in whom a human anti-endotoxin monoclonal antibody should work best.



Centoxin:

- Effective in significantly reducing mortality in both severely ill and less severely ill patients with:
  - shock and without shock[1]
  - high APACHE II scores (>25) and low APACHE II scores (≤25)[1]
- Safe and nonimmunogenic in clinical studies conducted to date[1,3]
- Administered in a single fixed dose regardless of disease severity, renal and hepatic function

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(HA-1A)

Saving lives in Gram-negative sepsis and septic shock

antibody formation is a possibility. Nevertheless, in clinical trials, anti-HA-1A antibodies were not detected (with a radioimmunoassay) in blood samples taken from patients up to 35 days after administration of a single dose of Centoxin. The immunogenic risk of repeated administration of Centoxin has not been extensively investigated. **Use During Pregnancy and Lactation** There has been no experience to date with the use of Centoxin in pregnant patients, and animal reproduction studies have not been conducted. Therefore, Centoxin should be used in pregnant patients only when, in the judgement of the physician, anticipated benefits outweigh the potential risks. It is not known if Centoxin is excreted in human milk. **Interaction with Other Medicaments and Other Forms of Interaction** There have been no reports of interactions between Centoxin and other drugs used concomitantly in the treatment of Gram-negative sepsis. **Overdose** The maximum amount of Centoxin that can safely be administered has not been determined. However, single doses as high as 300 mg of Centoxin have been safely administered to adults, and doses of 6 mg/kg up to a maximum of 100 mg to children from 10 months to 13 years of age. **Effects on Ability to Drive and Use Machines** HA-1A is pharmacologically inert and can therefore not be expected to affect the ability to drive and use machines. It is, in any case, administered only to hospitalized, seriously ill patients.

LEGAL CATEGORY POM

PACKAGE QUANTITIES Centoxin is available as a package containing 1 single dose 20 ml vial. **Product licence number** 8563/0010 **Basic NHS cost** £2,200. **Date of preparation** May 1991. For further information refer to data sheet or contact: Centocor Medical Services, Centocor B.V., Einsteinweg 101, 2333 CB Leiden, The Netherlands Tel. 0800-898458 © 1991 Centocor B.V. ® Registered Trademark. A 2001

References:

1. Ziegler EJ, Fisher CJ, Sprung CL, et al. N Engl J Med. 1991; 324: 429-436.
2. Wortel CH, van Deventer SJH, Sprung CL, et al. Presented at Fifth European Congress on Intensive Care Medicine; June 5-8, 1990, Amsterdam, The Netherlands.
3. Fischer, CJ Jr., Zimmerman J, Khazaeli MB, et al. Crit Care Med. 1990; 18: 1311-1315.

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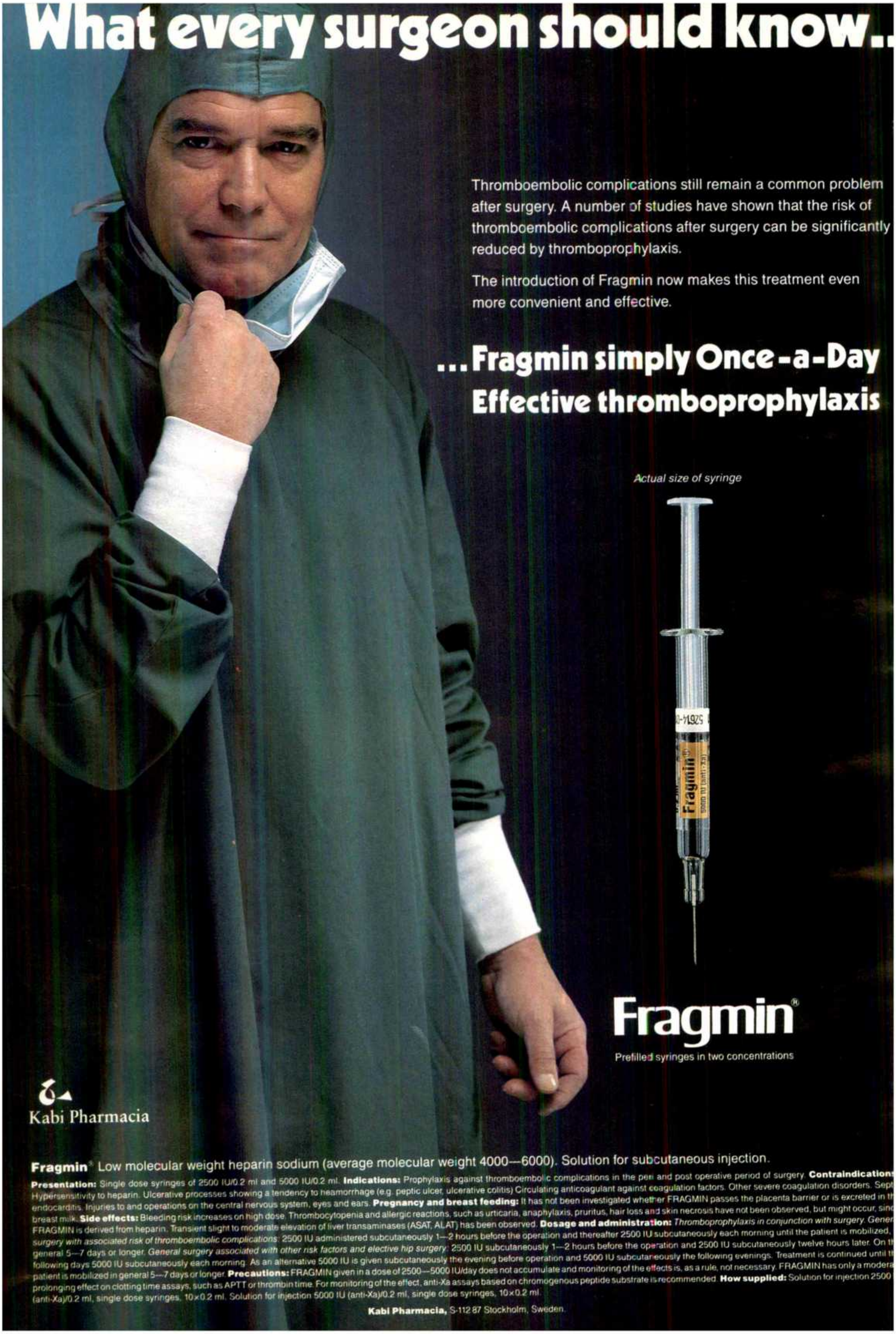

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Br. J. Surg. 1991, Vol. 78, September, 1025–6

Pelvic pouches

Pelvic pouch surgery has to some become the hallmark that distinguishes 'real' colorectal surgeons from 'the rest'. However, two considerations now make this assumption simplistic.

The first is the increasing ease of the procedure. Mucosectomy may not always be necessary, and long mucosectomy is certainly not warranted. Stapling removes much of the problem of the difficult pouch–anal anastomosis, and today there is a generation of surgeons, brought up on low pelvic dissection for colorectal cancer, who see little difficulty in applying this skill to colonic or ileal pelvic pouch surgery.

Pouch design remains with the Roman alphabet, and although I have suspected for some time that many of my finished products speak a different language, so long as they are big enough and any efferent limb is short enough, function seems reasonable. However, one should note that even short efferent limbs in S pouches and the lateral isoperistaltic pouch lengthen with time, causing late problems with catheterization and a need for revision in some. In general, large pouches are associated with a lower frequency of defaecation[1].

It is interesting to remember that pouch designs grew out of the earlier Kock pouch, where the particular intention (unsuccessful, as it turned out) was to create a bag in which peristaltic activity was minimized; the flaccid bag was to be emptied with a catheter at the patient's convenience. The hope was evanescent, and so came the nipple valve with all its attendant problems. Pelvic pouches anastomosed to the anus should not become flaccid bags if they are to continue to empty well, so there may yet be problems in store for the currently more popular S, J and W designs that are not isoperistaltic, and perhaps even for any reservoir that is too big, particularly if there is a pouch–anal anastomotic stenosis[2].

What about mucosectomy and endo–anal anastomosis[3]? This, perhaps more than anything else, remains the skill possessed by the 'real' colorectal surgeon and that skill is well worth possessing. Besides arguments based on cancer risk in dysplasia associated with ulcerative colitis, or in familial adenomatous polyposis (largely sterile arguments, to my mind, given the low risk when much larger areas of mucosa have been left behind after ileorectal anastomosis has been performed, and also given the much larger risk in familial adenomatous polyposis of dying of upper gastrointestinal cancer than of rectal cancer), there remains the question of what to do when for some reason or other one is left with a pouch in one's hand and an impossible or failed stapled anastomosis. The problem of the pouch not reaching the anus can largely be avoided by a trial descent and adoption of a short-limbed S pouch (which seems to empty satisfactorily, at least in the short term, and gives about 2 cm more length, which can at times be crucial), but there will always be the odd occasion where mucosectomy and endo–anal anastomosis is the only way out of a tight fix. A patient may reasonably expect this skill from a surgeon who chooses to perform the pouch operation himself or herself, rather than to refer the case to a colleague.

There remain areas of controversy, such as whether a defunctioning stoma should be *de rigeur* or not[4]; however, surgeons who have not managed to resolve this argument with low colorectal anastomosis are unlikely to reach agreement here either. Loop ileostomies have their own set of problems which must be offset against the frequency and consequences of an unprotected leak, either from the pouch itself or from the pouch–anal anastomosis.

The second consideration surrounding pelvic pouch surgery is its suitability. A patient with ulcerative colitis, with an aversion to hospitals, an encyclopaedic knowledge of public conveniences and a simple desire just to be well, may undergo major pouch surgery with an in-hospital complication rate of between 30 and 40 per cent[5], only to find urgency, frequency and regular outpatient attendance little changed. If similar results are seen in a patient with familial adenomatous polyposis, the rest of the family will abscond from screening before the surgeon can blink twice. The simpler colectomy with ileorectal anastomosis can supply as good results with a lower complication rate. Aylett[6] was prepared to use this operation in as many as 90 per cent of patients with ulcerative colitis coming to surgery; the cancer risk is

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as low as 5 per cent at 15 to 20 years, and failure might still allow a pelvic pouch to be offered to the patient. This also applies to patients with familial adenomatous polyposis.

There remain also the problems of pouchitis[7], indeterminate colitis[8] and Crohn's disease. Most surgeons would avoid constructing a pouch in Crohn's disease because complications are particularly frequent and the pouch may need to be excised, leaving the potential for a short gut after further future surgery for recurrent Crohn's disease. However, it is not always easy to exclude Crohn's disease: a prior colectomy specimen may be reported as showing ulcerative colitis, only to be reclassified as Crohn's disease by the pathologist, usually with a winsome smile, on subsequent examination of the specimen after a pouch has been constructed; the colon and rectum may even be diagnosed as showing ulcerative colitis only to find Crohn's disease subsequently in the pouch. This happens in about 5 per cent of pouches reported in the world literature and seems to be unavoidable. It remains intriguing to speculate whether the disease was always Crohn's disease in such cases, or whether Crohn's disease can develop in patients with previous ulcerative colitis.

For the future, the questions of pouch inflammation in a minority, of theoretical cancer risk in the 'colonized' pouch in ulcerative colitis and certainly in polyposis, and of longer term functional results of big floppy pouches ensure that pelvic pouch surgery will continue to generate a lot of interest.

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1. Nicholls RJ, Pezim ME. Restorative proctocolectomy with ileal reservoir for ulcerative colitis and familial adenomatous polyposis: a comparison of three reservoir designs. *Br J Surg* 1985; **72**: 470–4.
2. Fonkalsrud EW, Phillips JD. Reconstruction of malfunctioning ileoanal pouch procedures as an alternative to permanent ileostomy. *Am J Surg* 1990; **160**: 245–51.
3. O'Connell PR, Williams NS. Mucosectomy in restorative proctocolectomy. *Br J Surg* 1991; **78**: 129–30.
4. Everett WG. Experience of restorative proctocolectomy with ileal reservoir. *Br J Surg* 1989; **76**: 77–81.
5. Phillips RKS, Ritchie JK, Hawley PR. Proctocolectomy and ileostomy for ulcerative colitis: the longer term story. *J R Soc Med* 1989; **82**: 386–7.
6. Aylett SO. Three hundred cases of diffuse ulcerative colitis treated by total colectomy and ileorectal anastomosis. *Br Med J* 1966; **i**: 1001–5.
7. Madden MV, Farthing MJG, Nicholls RJ. Inflammation in ileal reservoirs: 'pouchitis'. *Gut* 1990; **31**: 247–9.
8. Pezim ME, Pemberton JH, Beart RW Jr *et al.* Outcome of 'indeterminant' colitis following ileal pouch–anal anastomosis. *Dis Colon Rectum* 1989; **32**: 653–8.

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Endothelium-derived relaxing factor and vein grafts

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Platelet thrombosis, intimal hyperplasia and progression of atherosclerosis are the most important factors determining the patency of vein grafts for arterial occlusive disease. Interactions between aggregating platelets and the vessel wall play an important role in all of these processes. Recently, it has become evident that the endothelium modulates the underlying vascular smooth muscle by releasing an endothelium-derived relaxing factor, a potent vasodilator and anti-aggregating substance. Little information is available, however, on such endothelial functions of autogenous vein grafts. This review focuses on vascular modulation by endothelium-derived relaxing factor in vein grafts.

The vascular endothelium is the monolayer of squamous cells in direct contact with circulating blood. Since the first report in 1980 by Furchgott and Zawadzki[1] of the endothelium dependency of acetylcholine-induced relaxation in isolated arteries, many findings have indicated that the intima significantly modulates the degree of contraction of the underlying vascular smooth muscle[2]. The vasoactive substances liberated from the endothelium include prostacyclin, a non-prostanoid endothelium-derived relaxing factor (EDRF), endothelium-derived hyperpolarizing factor[3–6] and endothelin[7]. The last is a peptide which may be isolated from cultured endothelial cells and which has a potent constrictor action on arterial and venous smooth muscle cells[7,8]. It has become evident that alterations in the endothelium-dependent responsiveness of vascular smooth muscle are involved in the pathogenesis of several cardiovascular diseases[5].

The autogenous vein graft is the most suitable conduit for reconstruction at many sites of arterial occlusive disease[9–11]. In the early postoperative period after graft insertion, besides technical difficulties, acute platelet thrombosis may lead to graft occlusion. Late occlusion results from intimal hyperplasia or progression of underlying atherosclerotic vascular disease[12–15]. Interactions between aggregating platelets and the vessel wall (endothelium and vascular smooth muscle) appear to play an important role in all three processes. EDRF not only relaxes vascular smooth muscle and reduces platelet adhesion[16], it is also a potent anti-aggregatory substance[17–19]. Furthermore, EDRF may be released in response to aggregating platelets and to certain products released from platelets[20,21]; the endothelium of veins may curtail the vasoconstriction induced by aggregating platelets by releasing EDRF[22], although endothelium-dependent relaxation is less pronounced in venous tissue than in arterial tissue[23–25]. This brief review describes the current status of experimental studies concerning the possible role of EDRF in the pathogenesis of vein graft occlusion.

Nature and physiology of EDRF

EDRF is a diffusible vasodilator[1] with a very short half-life in oxygenated buffer solution[26,27]. It is inactivated by superoxide anions and its half-life can be prolonged by superoxide dismutase, a scavenger of the oxygen-derived free radical[27], which indicates that EDRF is an oxidized substance and that the oxidized state is essential for its biological activity. One of the EDRF(s) has been identified as nitric oxide[28–30] or a donor of nitric oxide which is produced from L-arginine[31], although specific similarities and dissimilarities between EDRF and nitric oxide are still a matter of discussion[32,33].

The action of EDRF is mediated through the direct activation of soluble guanylate cyclase and hence the production of guanosine 3′,5′-cyclic monophosphate (c-GMP)[34,35], while prostacyclin is made through the production of adenosine 3′,5′-cyclic monophosphate (c-AMP)[36]. The elevation of cyclic-GMP levels in the smooth muscle cells and platelets relaxes the smooth muscle and inhibits platelet aggregation, respectively[37].

Role of EDRF in the pathophysiological state

One of the characteristics of a diseased vascular wall is the impairment of endothelium-dependent relaxation. This has been demonstrated repeatedly by several groups in animals with hypertension, in animals with atherosclerosis[38–41], and in experimental cerebral vasospasm[42]. The impairment, which is most pronounced for the relaxation produced by platelet products, is due to an inability of the endothelial cells to release EDRF. In these circumstances, the endothelium loses the ability to prevent vasospasm in response to platelet products such as serotonin, adenosine 5′-diphosphate (ADP) and thromboxane A_2, which are able to activate the vascular smooth muscle cells directly thereby producing contraction. In humans, atherosclerotic arteries lose their ability to relax when infused *in situ* with acetylcholine; instead, a paradoxical vasoconstriction occurs[43].

EDRF and vein graft

The reversed autogenous vein bypass graft is used extensively for the treatment of occlusive vascular disease. During the grafting procedure, the delicate endothelial cell layer is inevitably damaged to some extent. Current efforts in vascular surgery are now directed toward minimizing this disruption and damage[44]. While regeneration of the graft endothelial lining does occur[45], little information is available on the function of this regenerated intima.

Miller *et al.*[46] reported that grafting of autogenous femoral vein into the arterial circulation of the dog results in the selective loss of inhibitory endothelium-dependent response to acetylcholine in such a vein graft. The endothelial cells of canine vein graft are capable of producing an EDRF and the smooth muscle cells are capable of responding to such a factor because

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endothelium-derived inhibitory responses can be evoked by calcium ionophore, A23187, a substance that releases an endothelium-derived factor similar to that generated by acetylcholine, but by a process not associated with receptor activation[47]. However, not all receptor-mediated responses are lost in the endothelium of the canine vein graft, as is evidenced by the demonstration that ADP and thrombin evoke endothelium-dependent relaxation. The exact mechanism for the selective loss of the acetylcholine-induced relaxation in canine vein grafts remains unclear. Veins grafted into the carotid arterial circulation of rabbits and harvested 4 weeks after surgery do not respond to acetylcholine, histamine, ADP or aggregating platelets[48,49].

Endothelium-dependent relaxation in response to aggregating platelets in veins is the collective expression of the responses to several products released from platelets[21,22]. Platelet-induced relaxation in the rabbit jugular vein is mediated mainly by ADP with little contribution of serotonin[49], whereas in the porcine femoral vein platelet-induced relaxation is mediated by both ADP and serotonin[22]. In rabbit vein graft platelet-induced relaxation is converted to contraction because of reduced endothelium-dependent relaxation to ADP and augmented endothelium-independent contraction in response to serotonin[49,50].

Several possible mechanisms can be considered for the impairment of endothelium-dependent relaxation in vein grafts. First, the production and/or release of EDRF may be depressed. There is no doubt that the endothelium of venous grafts is capable of producing EDRF and that the response of smooth muscle cells to EDRF remains unaltered, because endothelium-dependent relaxation can be evoked by calcium ionophore A23187 in both rabbit and canine venous grafts, and by ADP and thrombin in canine vein grafts[46,49]. However, the production of EDRF may be reduced as suggested by the experiments of Komori *et al.* using rabbit vein grafts[49]. Further detailed bioassay experiments are called for to elucidate this matter fully.

The second possible mechanism for impairment of relaxation is that the smooth muscle may not respond to EDRF. Komori *et al.*[49] reported that in rabbit vein graft the sensitivity of the smooth muscle to nitric oxide, a major EDRF[28], is reduced. However, EDRF purified from bovine aortic endothelial cells caused a significant degree of relaxation in rabbit vein graft[48]. In such tissues, the relaxation elicited by SIN-1 (the activated metabolite of molsidomine[51,52]) was also reduced[49]. SIN-1 relaxes the smooth muscle by releasing nitric oxide[53–55]. A decrease in sensitivity to contractile agents such as noradrenaline and prostaglandin $F_{2\alpha}$ is also evident in vein grafts[49,50]. All of these reports suggest that the smooth muscle of vein grafts becomes less sensitive to both excitatory and inhibitory stimuli[49,50].

The third possible mechanism is that the production of cyclic-GMP in vein graft smooth muscle may be impaired. EDRF not only relaxes vascular smooth muscle, but also reduces platelet adhesion[16] and is itself a potent anti-aggregatory substance[17–19]. These actions of EDRF are mediated by an increased production of cyclic-GMP through the direct activation of soluble guanylate cyclase[34,36,37,56]. However, that vein grafts have an impaired cyclic-GMP production is unlikely. Although in rabbit vein grafts the endothelium-mediated production of cyclic-GMP (basal and stimulated by acetylcholine) is significantly reduced when compared with controls, that evoked by SIN-1 remains unchanged[57] and so the potency of smooth muscles to produce cyclic-GMP would seem to remain unaltered in vein grafts.

The fourth possible mechanism may be that the diffusion of EDRF to the underlying smooth muscle is impaired in vein grafts. This possibility is probable because an intimal thickening is observed in vein grafts. Such thickening could act as a diffusion barrier against EDRF which has a very short half-life[2,24]. The extent of intimal thickening in reducing the diffusion of EDRF is, however, still controversial[58].

In summary, the decrease in the endothelium-dependent relaxing response of smooth muscles observed in vein grafts may be related to the alteration of several factors occurring in both endothelial and smooth muscle cells. One might tentatively suggest that at least three factors are involved: a decrease in the amount of released EDRF, a decreased sensitivity of smooth muscle cells to EDRF, and a decreased diffusion of EDRF due to intimal thickening.

Clinical significance

The autogenous vein bypass graft is an important method in the treatment of coronary and peripheral arterial occlusions. If technical problems are excluded, early graft failure can normally be attributed mainly to platelet thrombosis due to a low flow rate and to the thrombogenicity of the graft and host vessels. In the intact endothelium, EDRF released from the endothelium inhibits the aggregation of platelets by raising platelet levels of cyclic-GMP (*Figure 1*). Any decrease in release and/or production of EDRF would reduce the negative feedback effect of EDRF which might cause platelet adhesion to the vessel wall, aggregation of platelets, and facilitate the occlusion of the vein graft (*Figure 2*).

It remains unclear whether or not the vasospasm plays a significant role in vein graft failure. However, several angiographic reports have suggested an involvement of spasm in grafted vein[59–61]. It is likely that reduced production of EDRF in the vein is causally related to such graft spasm.

An additional aetiology of late graft failure is atherosclerotic development which may be related, in part, to a decreased production of EDRF. Impaired endothelium-dependent relaxation in hypercholesterolaemia or atherosclerosis has been reported in the rabbit aorta[38–40], monkey, porcine iliac artery[41,62] and human coronary artery[39,43]. These studies have suggested that decreased production of EDRF from the damaged endothelial cell might predispose the vessel to the formation of atherosclerosis. Thus, an alteration in the release

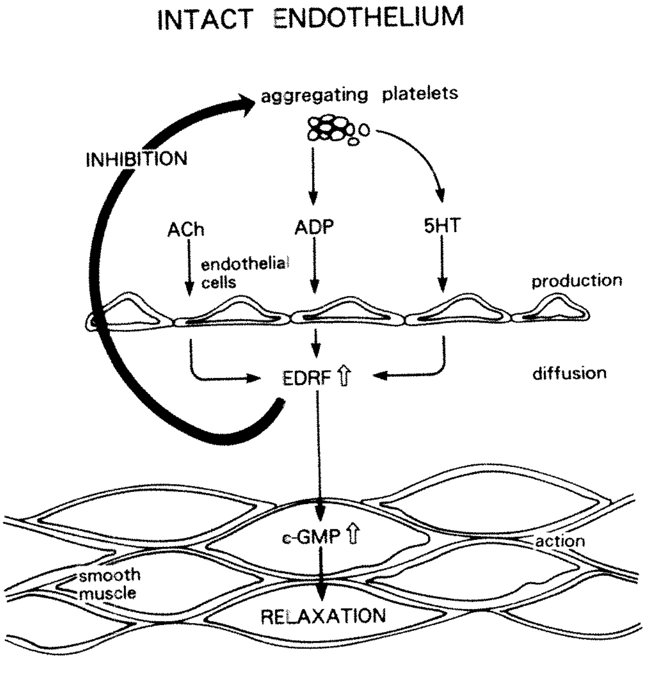

Figure 1 *Several effects of endothelium derived relaxing factor (EDRF) during platelet aggregation. Endothelium dependent relaxation to aggregating platelets is achieved mainly by adenosine 5'-diphosphate (ADP) with a little contribution from serotonin (5HT), although this depends on the species. Under normal conditions in the presence of the intact endothelium, EDRF may act against platelet aggregation by causing an increase in the concentration of guanosine 3',5'-cyclic monophosphate (c-GMP) in platelets. ACh, acetylcholine*

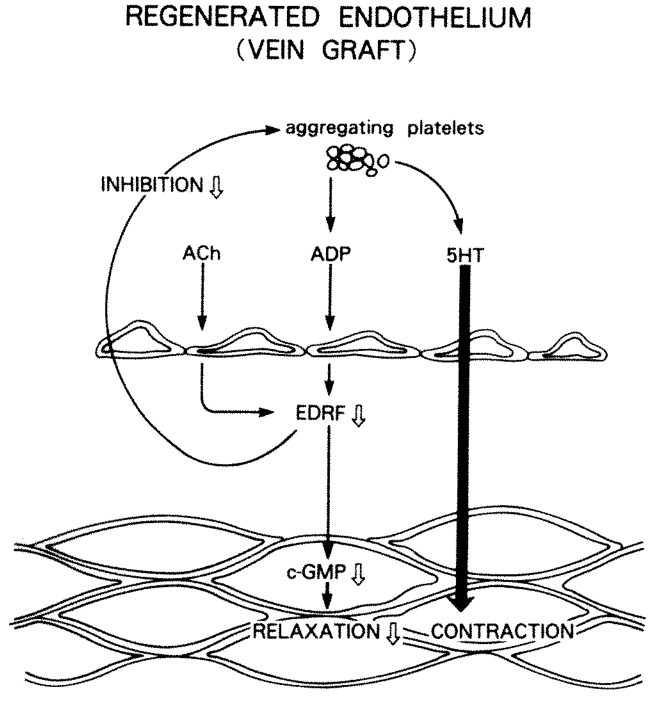

Figure 2 *Endothelium-dependent response under pathological conditions. The endothelium is dysfunctional, releasing less endothelium-derived relaxing factor (EDRF), while the ability of the smooth muscles to contract is augmented. As a result, contraction predominates. In a vein graft, the decreased release and/or production of EDRF would decrease the negative feedback effect of EDRF, thereby causing platelet adhesion to the vessel wall and aggregation of the platelets. ACh, acetylcholine; ADP, adenosine 5'-diphosphate; 5HT, 5-hydroxytryptamine (serotonin); c-GMP, guanosine 3',5'-cyclic monophosphate*

of EDRF by vein grafts may explain the sensitivity of such grafts to both platelet-mediated thrombosis and atherosclerosis.

Discussion

It is suggested that the neo-endothelium in the vein graft is functionally abnormal. This is mainly due to an alteration in the production and action of EDRF in response to certain agonists and aggregating platelets, in spite of the absence of any morphological change in the venous endothelium. The endothelial dysfunction causing decreased release of EDRF may predispose the vein graft to platelet-mediated thrombosis, atherosclerosis and, ultimately, graft failure. A normal endothelial function in autogenous *arterial* grafts may explain their superior patency rates when compared with autogenous vein grafts[25,63].

It seems likely that preservation of endothelial function is beneficial in preventing graft spasm and occlusion, but the topic is still poorly understood. Detailed experiments to elucidate the further possible role of EDRF as well as to establish the actions of additional factors contributing to vein graft occlusion need to be carried out. We suggest that changes in flow velocity, compliance mismatch and the development of atherosclerosis should also be considered in this context.

Acknowledgements

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References

1. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature* 1980; **288**: 373–6.
2. Furchgott RF. Role of endothelium in responses of vascular smooth muscle. *Circ Res* 1983; **53**: 557–73.
3. Komori K, Suzuki H. Electrical responses of smooth muscle cells during cholinergic vasodilation in the saphenous artery. *Circ Res* 1987; **61**: 586–93.
4. Chen G, Suzuki H, Weston AH. Acetylcholine releases endothelium-derived hyperpolarizing factor and EDRF from rat blood vessels. *Br J Pharmacol* 1988; **95**: 1165–74.
5. Vanhoutte PM. The endothelium: modulator of vascular smooth-muscle tone. *N Engl J Med* 1988; **319**: 512–13.
6. Komori K, Vanhoutte PM. Endothelium-derived hyperpolarizing factor. In: Vanhoutte PM, ed. *Proceedings of the Fifth International Symposium: 'Mechanisms of Vasodilatation'.* Karger, 1990; **27**: 238–45.
7. Yanagisawa M, Kurihara H, Kimura S *et al.* A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature* 1988; **332**: 411–15.
8. Miller VM, Komori K, Burnett JC, Vanhoutte PM. Differential sensitivity to endothelin in canine arteries and veins. *Am J Physiol* 1989; **257**: H1127–31.
9. Brewster DC, LaSalle AJ, Robinson JG, Strayhorn EC, Darling CR. Factors affecting patency of femoropopliteal bypass grafts. *Surg Gynecol Obstet* 1983; **157**: 437–42.
10. Szilagyi DE, Hageman JH, Smith RF, Elliott JP, Brown F, Dietz P. Autogenous vein grafting femoropopliteal atherosclerosis. *Surgery* 1979; **86**: 836–51.
11. Deweese JA, Rob CHG. Autogenous venous grafts ten years later. *Surgery* 1977; **82**: 775–84.
12. Chesebro JH, Fuster V. Drug trials in prevention of occlusion of aortocoronary artery vein grafts. *J Thorac Cardiovasc Surg* 1982; **83**: 90–3.
13. Kinley CE, Marble ARE. Compliance: a continuing problem with vascular grafts. *J Cardiovasc Surg* 1980; **21**: 163–70.
14. Gunstensen J, Smith RC, El-Maraghi, Julian J, Belbeck L. Intimal hyperplasia in autogenous veins used for arterial replacement. *Can J Surg* 1982; **25**: 158–61.
15. Karayannacos PE, Hostetler JR, Bond MG *et al.* Late failure in vein grafts; mediating factors in subendothelial fibromuscular hyperplasia. *Ann Surg* 1978; **287**: 183–8.
16. Sneddon JM, Vane JR. Endothelium-derived relaxing factor reduces platelet adhesion to bovine endothelial cells. *Proc Natl Acad Sci, USA* 1988; **85**: 2800–4.
17. Azuma H, Ishikawa M, Sekizaki S. Endothelium-dependent inhibition of platelet aggregation. *Br J Pharmacol* 1986; **88**: 411–14.
18. Furlong B, Henderson AH, Lewis MJ, Smith JA. Endothelium-derived relaxing factor inhibits *in vitro* platelet aggregation. *Br J Pharmacol* 1987; **90**: 687–92.
19. Radomski MW, Palmer RMJ, Moncada S. Comparative pharmacology of endothelium-derived relaxing factor, nitric oxide and prostacyclin in platelets. *Br J Pharmacol* 1987; **92**: 181–7.
20. Cohen RA, Shepherd JT, Vanhoutte PM. Inhibitory role of the endothelium in the response of isolated coronary arteries to platelets. *Science* 1983; **221**: 273–4.
21. Vanhoutte PM, Houston DS. Platelets, endothelium and vasospasm. *Circulation* 1985; **72**: 728–34.
22. Komori K, Shimokawa H, Vanhoutte PM. Endothelium-dependent relaxation in response to aggregating platelets in porcine femoral veins and its modulation by diet. *Circulation* 1989; **80**: 401–9.
23. DeMay JG, Vanhoutte PM. Heterogeneous behavior of the canine arterial and venous wall. *Circ Res* 1982; **51**: 439–47.
24. Vanhoutte PM, Rubanyi GM, Miller VM, Houston DS. Modulation of vascular smooth muscle contraction by the endothelium. *Annu Rev Physiol* 1986; **48**: 307–20.
25. Luscher TF, Diederich D, Siebenmann R *et al.* Difference between endothelium-dependent relaxation in arterial and in venous coronary bypass grafts. *N Engl J Med* 1988; **319**: 462–7.
26. Griffith TM, Edwards DH, Lewis MJ, Newby AC, Henderson AH. The nature of endothelium-derived relaxing factor. *Nature* 1984; **308**: 645–7.
27. Gryglewski RJ, Palmer RMJ, Moncada S. Superoxide anion is involved in the breakdown of endothelium-derived relaxing factor. *Nature* 1986; **320**: 454–6.
28. Palmer RMJ, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature* 1987; **327**: 524–6.
29. Furchgott RF. Studies on relaxation of rabbit aorta by sodium nitrite: the basis for the proposal that the acid-activatable inhibitory factor from bovine retractor penis is inorganic nitrite and the endothelium-derived relaxing factor is nitric oxide. In: Vanhoutte PM, ed. *Mechanisms of Vasodilatation.* New York:

Raven Press, 1988: 401–14.

30. Ignarro LJ, Byrns RE, Wood KS. Biochemical and pharmacological properties of endothelium-derived relaxing factor and its similarity to nitric oxide radical. In: Vanhoutte PM, ed. *Mechanisms of Vasodilatation*. New York: Raven Press, 1988: 427–35.
31. Myers PR, Minor RJ Jr, Guerra R Jr, Bates JN, Harrison DG. Vasorelaxant properties of the endothelium-derived relaxing factor more closely resemble S-nitrosocysteine than nitric oxide. *Nature* 1990; **345**: 161–3.
32. Shikano K, Ohlstein EH, Berkovitz BA. Differential selectivity of endothelium-derived relaxing factor and nitric oxide in smooth muscle. *Br J Pharmacol* 1987; **92**: 483–5.
33. Komori KR, Lorenz RR, Vanhoutte PM. Nitric oxide, ACh, and electrical and mechanical properties of canine arterial smooth muscle. *Am J Physiol* 1988; **255**: H207–12.
34. Holzmann S. Endothelium-induced relaxation by acetylcholine associated with larger rises in cyclic GMP in coronary arterial strips. *J Cyclic Nucl Res* 1982; **8**: 409–19.
35. Rapoport RM, Murad F. Agonist-induced endothelium-dependent relaxation in rat thoracic aorta may be mediated through cyclic GMP. *Circ Res* 1983; **52**: 352–7.
36. Moncada S. Biological importance of prostacyclin. *Br J Pharmacol* 1982; **76**: 3–31.
37. Vane JR, Anggard EE, Botting RM. Regulatory functions of the vascular endothelium. *N Engl J Med* 1990; **323**: 27–36.
38. Verbeuren TJ, Jordaens RH, Zonnekeyn LL, Van Hove CE, Coene MC, Herman AG. Effect of hypercholesterolemia on vascular reactivity in the rabbit. I. Endothelium-dependent and endothelium-independent contractions and relaxations in isolated arteries of control and hypercholesterolemic rabbits. *Circ Res* 1986; **58**: 552–64.
39. Bossaler C, Hbib GB, Yamamoto H, Williams C, Wells S, Henry PD. Impaired muscarinic endothelium-dependent relaxation and cyclic guanosine 5′-monophosphate formation in atherosclerotic human coronary artery and rabbit aorta. *J Clin Invest* 1987; **79**: 170–4.
40. Jayakody L, Senartne M, Thompson A, Kappagoda T. Endothelium-dependent relaxation in experimental atherosclerosis in the rabbit. *Circ Res* 1987; **60**: 251–64.
41. Frieman RC, Mitchell GG, Heistad DD, Armstrong ML, Harrison DG. Atherosclerosis impairs endothelium-dependent vascular relaxation to acetylcholine and thrombin in primates. *Circ Res* 1986; **58**: 783–9.
42. Kim P, Sundt TM, Vanhoutte PM. Alterations in endothelium-dependent responsiveness of the canine basilar artery after subarachnoid hemorrhage. *J Neurosurg* 1989; **70**: 108–14.
43. Ludmer PL, Selwyn AP, Shook TL *et al*. Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries. *N Engl J Med* 1986; **315**: 1046–51.
44. Cambria RP, Megerman J, Abbott WM. Endothelial preservation in reversed and *in situ* autogenous vein grafts. *Ann Surg* 1985; **202**: 50–5.
45. Zwolak RM, Adams MC, Clowes AW. Kinetics of vein graft hyperplasia: association with tangential stress. *J Vasc Surg* 1987; **5**: 126–36.
46. Miller VM, Reigel MM, Hollier LH, Vanhoutte PM. Endothelium-dependent responses in autogenous femoral veins grafted into the arterial circulation of the dog. *J Clin Invest* 1987; **80**: 1350–7.
47. Furchgott RF, Jothianandan D, Cherry PD. Endothelium-dependent responses: the last three years. *Bibl Cardiol* 1984; **38**: 1–15.
48. Cross KS, El-Sanadiki MN, Murray JJ, Mikat EM, McCann RL, Hagen PO. Functional abnormalities of experimental autogenous vein graft neoendothelium. *Ann Surg* 1988; **208**: 631–8.
49. Komori K, Gloviczki P, Bourchier RG, Miller VM, Vanhoutte PM. Endothelium-dependent relaxations in response to aggregating platelets are impaired in reversed vein graft. *J Vasc Surg* 1990; **12**: 139–47.
50. Makhoul RG, Davis WS, Mikat EM, McCann RL, Hagen PO. Responsiveness of vein bypass grafts to stimulation with norepinephrine and 5-hydroxytryptamine. *J Vasc Surg* 1987; **6**: 32–8.
51. Bohme E, Grossman G, Spies C. Effects of molsidomine and other NO-containing vasodilators on cyclic GMP formation. *Eur Heart J* 1983; **4**: 19–24.
52. Komori K, Vanhoutte PM. Effects of SIN-1 on electrical and mechanical properties in the canine saphenous vein. *J Cardiovasc Pharmacol* 1989; **14**: S62–6.
53. Feelish M, Noack EA. Correlation between nitric oxide formation during degradation of organic nitrates and activation of guanylate cyclase. *Eur J Pharmacol* 1987; **139**: 19–30.
54. Arnold WP, Mittal CK, Katsuki S, Murad F. Nitric oxide activates guanylate cyclase and increases guanosine 3′5′-cyclic monophosphate levels in various tissues. *Proc Natl Acad Sci USA* 1977; **74**: 3202–7.
55. Katsuki S, Arnol W, Mittal C, Murad F. Stimulation of guanylate cyclase by sodium nitroprusside, nitroglycerin and nitric oxide in various tissue preparations and comparison to the effects of sodium azide and hydroxylamine. *J Cyclic Nucl Res* 1977; **3**: 23–35.
56. Diamond J, Chu EB. Possible role for cyclic GMP in endothelium-dependent relaxation of rabbit aorta by acetylcholine: comparison with nitroglycerin. *Res Commun Chem Pathol Pharmacol* 1983; **41**: 369–81.
57. Komori K, Schini VB, Gloviczki P, Bourchier RG, Vanhoutte PM. The impairment of endothelium dependent relaxations in reversed vein grafts is associated with a reduced production of cyclic GMP. *J Vasc Surg* 1991 (in press).
58. Harrison DG, Armstrong ML, Frieman PC, Heistad DD. Restoration of endothelium-dependent relaxation by dietary treatment of atherosclerosis. *J Clin Invest* 1987; **80**: 1808–11.
59. Victor MF, Kimbris D, Iskandrian AS *et al*. Spasm of a saphenous vein bypass graft: a possible mechanism for occlusion of the vein graft. *Chest* 1981; **80**: 413–15.
60. Walinski P. Angiographic documentation of spontaneous spasm of saphenous vein coronary bypass graft. *Am Heart J* 1982; **103**: 290–2.
61. D'Souza VJ, Valasquez G, Kahl FR, Hackshaw BT, Amplats BK. Spasm of the aortocoronary venous graft. *Radiology* 1984; **151**: 83–4.
62. Komori K, Shimokawa H, Vanhoutte PM. Hypercholesterolemia impairs endothelium-dependent relaxations to aggregating platelets in porcine iliac arteries. *J Vasc Surg* 1989; **10**: 318–25.
63. El-Sanadiki MN, Cross KS, Murray JJ, Mikat EM, McCann RL, Hagen PO. Normal endothelial function and decreased vasoreactivity of experimental arterial grafts. *J Vasc Surg* 1988; **8**: 98–106.

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Postsplenectomy sepsis and its mortality rate: actual *versus* perceived risks

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A collective critical review of the literature on postsplenectomy sepsis from 1952 to 1987 has been undertaken. The reports cover a cohort of 12 514 patients undergoing splenectomy but of these only 5902 reports were sufficiently detailed to allow a useful analysis. The incidence of infection after splenectomy in children under 16 years old was 4·4 per cent with a mortality rate of 2·2 per cent. The corresponding figures for adults were 0·9 per cent and 0·8 per cent respectively. The present analysis of well documented patients has shown that severe infection after splenectomy for benign disease is very uncommon except in infants (infection rate 15·7 per cent) and children below the age of 5 years (infection rate 10·4 per cent). Many of these reported postsplenectomy infections may have been coincidental. It is also apparent that children contract a different type of infection after splenectomy than adults, predominantly a meningitis which is less frequently fatal. Adults, in contrast, appear to develop a septicaemic type of illness associated with a higher mortality rate. This survey has also shown that children are reported to be no more susceptible to pneumococcal sepsis than to infection caused by any other organism. Although the removal of the spleen in otherwise normal people does not appear to be associated with an increased frequency of infection, the presence of a coexistent disorder, notably hepatic disease, can increase the risk substantially.

In 1919, Morris and Bullock[1] concluded that removal of the spleen in humans may lead to an increased susceptibility to infection and cautioned against indiscriminate removal of the organ. The first reported case of postsplenectomy infection was by O'Donnell[2] in 1929, but it was not until 1952 that attention focused on the subject when King and Shumacker reported five cases of severe infection in infants less than 1 year old who had undergone splenectomy for spherocytosis[3]. The current consensus view is that splenectomy is accompanied by an increased risk of sepsis, especially in children, and this is caused predominantly by *Streptococcus pneumoniae*.

The incidence of infection after splenectomy is usually quoted from the major collective review of Singer[4], who evaluated 2795 patients. These data were later updated in a combined study group of 4208 patients[5]. The only prospective study on the incidence of infection was reported by Walker[6] who observed 16 severe infections in 821 children undergoing splenectomy in a 4-year period with a 70 per cent 5-year follow-up. Walker recommended that elective splenectomy for congenital spherocytosis and idiopathic thrombocytopenic purpura be delayed until the age of 3 years.

Despite the voluminous literature, the true incidence of postsplenectomy infection, its nature, the risk in different age groups, and the effect of underlying conditions for which the spleen is removed all remain unsettled. Some surgeons regard the risk as significant and argue strongly for a conservative management in splenic trauma. Others believe that postsplenectomy infection is overstated and estimate that the risk of increased transfusion requirements in these patients outweighs the potential septic sequelae of the asplenic state. The present collective review of the literature on the subject was undertaken to reappraise the problem, with particular emphasis on age and disease-related factors of postsplenectomy infection.

Patients and methods

The reports of patients undergoing splenectomy published between 1952 and 1987 have been reviewed. Only those series that made reference to infection as a complication of splenectomy were included. The first part of this survey was conducted on a cohort of 12 514 patients drawn from 59 reported series[3,4,6–62]. Three reported series were excluded because of insufficient information relating to the indications for splenectomy, age specification at operation, interval to infection and nature of infecting organisms[63–65].

In the second part of the survey, the well documented reported infections which developed after splenectomy (349 septic episodes in 316 patients) were analysed in detail to assess the nature and characteristics of postsplenectomy infection. This group consisted of 173 patients suffering 199 infections drawn from the 12 514 cohort from the reported series and an additional 143 patients with 150 septic episodes published as individual case reports[66–140].

In this study, severe infections were defined as septicaemia, meningitis and severe or recurrent pneumonia. Minor infections, viral illnesses, protozoal infections and infections that could be regarded as postoperative complications were excluded.

Results

Overall incidence of infection

Among the 12 514 patients undergoing splenectomy for all indications, there were 447 severe infections (3·6 per cent) and 221 deaths (1·8 per cent) reported by the authors. As many of these reports gave few details of the infections or omitted any reference to non-fatal infections, these figures are likely to be inaccurate. A more reliable estimate of the overall incidence of

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Table 1 *Overall incidence of reported postsplenectomy infection and mortality in well documented cases* (n = *5902*)

Age group (years)	Patients	Infections	Deaths
Children < 16	2974	131 (4·4)	66 (2·2)
Adults > 16	1782	16 (0·9)	15 (0·8)
Not specified	1146	26 (2·3)	10 (0·9)
Total	5902	173 (2·9)	91 (1·5)

Values in parentheses are percentages

Table 2 *Incidence of postsplenectomy sepsis and mortality related to the principal indication for operation. Data based on 3952 well documented patients*

Indication for splenectomy	Patients	Infections	Deaths
Trauma			
Total	1358*	21 (1·5)	10 (0·7)
< 16 years	883*	18 (2·0)	9 (1·0)
> 16 years	395*	0	0
Incidental	420	5 (1·2)	5 (1·2)
Spherocytosis			
Total	932	22 (2·4)	14 (1·5)
< 16 years	707	21 (3·0)	13 (1·8)
ITP			
Total	484	16 (3·3)	7 (1·4)
< 16 years	384	14 (3·6)	6 (1·6)
Hodgkin's disease (total)	451	32 (7·1)	16 (3·5)
Thalassaemia			
Total	185	13 (7·0)	9 (4·9)
< 16 years	168	13 (7·7)	9 (5·4)
Portal hypertension (total)	122	5 (4·1)	3 (2·5)

Values in parentheses are percentages; ITP, idiopathic thrombocytopenic purpura; * 80 patients undergoing splenectomy for trauma could not be classified according to age[44,50]. These accounted for three infections and one death

Table 3 *Incidence of sepsis and mortality in infants after splenectomy. Based on 795 children undergoing the operation under 5 years old*

Series	Age (years)	Patients	Infections	Deaths
Present review	< 5	795	83 (10·4)	36 (4·5)
Present review	< 1	134	21 (15·7)	9 (6·7)
Broberger *et al.*[15]	< 1	56	13 (23·2)	7 (12·5)
Erickson *et al.*[30]	< 1	68	12 (17·6)	6 (8·8)

Values in parentheses are percentages

infection and mortality was obtained from consideration of the fully documented reported series[3,4,7–51] amounting to 5902 patients, 173 of whom developed severe infection (2·9 per cent) and 91 of whom died (1·5 per cent). A significantly higher incidence of postsplenectomy infection and mortality in children (4·4 per cent and 2·2 per cent respectively) compared with adults (0·9 per cent and 0·8 per cent) was confirmed (*Table 1*; $\chi^2 = 46·1$ and $\chi^2 = 12·6$ respectively; both $P < 0·001$).

Effect of underlying disease on incidence of infection. The incidence of infection in relation to the principal indications for splenectomy is shown in *Table 2*. These values are derived from the 5902 patients undergoing splenectomy with complete information. The incidence of infection was observed to be higher in those under 16 years for all these indications for splenectomy. A particularly high incidence of infection after splenectomy for thalassaemia and Hodgkin's disease was confirmed, both being significantly higher than the incidence after splenectomy for trauma ($\chi^2 = 22·7$ and $\chi^2 = 36·9$ respectively; both $P < 0·001$).

Incidence of infection in infancy and childhood. Table 3 outlines the morbidity and mortality rates from postsplenectomy sepsis in this age group. It can be seen that the incidence of severe infection in infants was 15·7 per cent and the mortality rate from infection 6·7 per cent. The corresponding values for children under 5 years were 10·4 per cent and 4·5 per cent respectively.

Characteristics of postsplenectomy infection

The second part of this survey was based on analysis of 349 septic episodes in 316 patients defined previously. Eighteen of these infections occurred in 18 patients diagnosed as asplenic due either to congenital absence of the spleen or splenic atrophy[66–78,131] (L. D. Gruer and A. M. Geddes, personal communication).

Causative organisms. The principal organisms reported as causing severe infection after splenectomy are outlined in *Table 4*. The single most important organism responsible for postsplenectomy sepsis was *Streptococcus pneumoniae*, accounting for 57 per cent of infections and 59 per cent of deaths. In comparison, infections caused by other organisms were infrequent. Only 22 septic episodes were caused by the second commonest organism, *Haemophilus influenzae*, with a mortality rate of 32 per cent. Nineteen *Haemophilus* infections occurred in children under 15 years of age (86 per cent), ten infections being meningitis. There were only 13 reported infections caused by *Neisseria meningitidis*, the third commonest cause of infection. Although uncommon, *Escherichia coli* and *Pseudomonas* infections carried the highest mortality rates (77 and 78 per cent respectively). A curious infection caused by an unidentified Gram-negative bacillus has been reported three times in a total of seven patients[89–91]. It is often associated with dog bites, and those without a spleen appear to be particularly susceptible[89]. In 15 per cent of infections no organism was identified.

Age of patients at the onset of infection. The frequency of postsplenectomy infections at different ages in this collective review is shown in *Table 5*. Irrespective of age at operation, 52 per cent of first infections occurred in patients under 15 years and 22 per cent in children under 5 years of age. However, no age group was immune and 8 per cent of infections were reported in people over 60 years of age. Although there was no definite predisposition to pneumococcal infections in any specific age group, the percentage of infections caused by this

Table 4 *Organisms responsible for 349 episodes of postsplenectomy infection*

Organism	Total infection	Deaths: Total	Deaths: Percentage of total infections	Deaths: Percentage infected due to organism
Streptococcus pneumoniae	198 (56·7)	114	32·7	57·6
Haemophilus influenzae	22 (6·3)	7	2·0	31·8
Escherichia coli	13 (3·7)	10	2·9	76·9
Neisseria meningitidis	13 (3·7)	8	2·3	61·5
Streptococci	11 (3·1)	3	0·8	27·3
Pseudomonas	9 (2·6)	7	2·0	77·8
Staphylococci	7 (2·0)	2	0·6	28·6
Gram-negative bacilli	7 (2·0)	2	0·6	28·6
Miscellaneous	18 (5·2)	9	2·5	50·0
Unknown	51 (14·6)	31	8·8	62·0
Total	349	193	55·3	

organism tended to rise progressively with age. Thus only 39 per cent of infections in those under 5 years were pneumococcal, compared with 71 per cent of infections in those over 20 years of age.

Interval from splenectomy to infection. Infections were most frequent in the first and second years after splenectomy (*Table 6*). One-third (32 per cent) of all first infections occurred within the first year of operation and just over half (52 per cent) within 2 years. However, 33 per cent of pneumococcal infections occurred at least 5 years after splenectomy.

Table 5 *Frequency of first infections at different ages of patients at time of infection. Data based on 281 first episodes of infection where full details were available*

Age (years)	All infections	Pneumococcal infections	Percentage pneumococcal of all infections
<5	62 (22·1)	24 (15·0)	38·7
6–10	49 (17·4)	28 (17·5)	57·1
11–15	34 (12·1)	20 (12·5)	58·8
16–20	18 (6·4)	4 (2·5)	22·2
21–30	31 (11·0)	22 (13·8)	71·0
31–40	25 (8·9)	20 (12·5)	80·0
41–50	23 (8·2)	15 (9·4)	65·2
51–60	17 (6·0)	9 (5·6)	52·9
>61	22 (7·8)	18 (11·3)	81·8
Total	281	160 (56·9)	

Values in parentheses are percentages

Table 6 *Interval to first infection. Based on 288 individual patients with full details*

Interval from splenectomy	All infections	Pneumococcal infections
0–6 months	50 (17·4)	23 (14·4)
7–12 months	41 (14·2)	18 (11·3)
1–2 years	59 (20·5)	33 (20·6)
2–3 years	25 (8·7)	13 (8·1)
3–4 years	25 (8·7)	18 (11·3)
4–5 years	13 (4·5)	3 (1·9)
5–10 years	48 (16·7)	34 (21·3)
11–15 years	16 (5·5)	10 (6·3)
16–20 years	2 (0·7)	2 (1·3)
>20 years	9 (3·1)	6 (3·8)
Total	288	160

Values in parentheses are percentages

There was a relationship between the age at splenectomy and the interval to subsequent infection, with a significant positive correlation between age at surgery and interval to both pneumococcal infection (Spearman's rank correlation, $r_S = 0{\cdot}288$, $P = 0{\cdot}003$) and infection caused by other organisms ($r_S = 0{\cdot}398$, $P < 0{\cdot}0001$). Therefore, the younger the patient at splenectomy, the shorter the interval to infection.

Relationship between age and type of postsplenectomy infection. The type of infection also varied with the age of the patient (*Table 7*). Over 90 per cent (259 of 281) of first infections were either septicaemia or meningitis. Pure meningitis without septicaemia carried an overall mortality rate of 22 per cent (14 of 65 cases) and 83 per cent of cases of pure meningitis occurred in children under 15 years, with a 17 per cent mortality rate in this age group (nine of 54 cases).

In contrast, septicaemia was encountered in all age groups and was associated with a 65 per cent mortality rate (101 of 156 cases). When septicaemia complicated meningitis, this too was fatal in 76 per cent (29 of 38 cases). Postsplenectomy meningitis in adults was more frequently associated with septicaemia (23 of 34 cases), with a consequent higher mortality rate (19 of 23 cases) than was the case in children.

When pneumococcal infections were considered separately, it was observed that these infections after splenectomy carried a lower mortality rate in infants and children than in adults. In children under 10 years the mortality rate from pneumococcal infection was 44 per cent (23 of 52 cases), falling to 37 per cent below 5 years (nine of 24 cases) and 25 per cent below 3 years of age (four of 16 cases). In contrast, the mortality rate from pneumococcal infection in people over 15 years old was 67 per cent (59 of 88 cases), remaining constant with increasing age.

Infection in children under 5 years old. A total of 62 children were reported as having severe infections before their fifth birthday. Only nine (15 per cent) of these died from pneumococcal sepsis. Of these nine children, three had pneumococcal meningitis, five septicaemia and one endocarditis. Five of these children were aged between 3 and 5 years at the time of infection. A further 34 per cent (21 of 62) of children died from infections caused by other bacteria; in 12 cases organisms were never identified. The principal cause of death from infection in children under 5 years was septicaemia caused by organisms other than the pneumococcus, which accounted for 17 of 30 deaths (57 per cent).

Table 7 *Number of specific infections at various age groups. Based on 281 well documented first infections*

Age (years)	Only meningitis ($n = 65$)		Septicaemia and meningitis ($n = 38$)		Only septicaemia ($n = 156$)		Other infections ($n = 22$)	
	Pn	Other	Pn	Other	Pn	Other	Pn	Other
<3	10(1)	11(2)	0	1(1)	6(3)	13(12)	0	3(2)
3–5	5(2)	2(0)	0	1(1)	2(2)	6(3)	1(1)	1(0)
6–10	13(3)	5(0)	5(4)	1(1)	10(7)	9(5)	0	6(3)
11–15	4(1)	4(0)	7(3)	0	9(6)	6(4)	0	4(3)
16–20	0	1(0)	1(1)	0	3(3)	9(5)	0	4(1)
21–30	2(0)	1(1)	3(2)	1(0)	16(10)	6(3)	1(0)	1(0)
31–40	2(1)	0	5(5)	1(1)	13(9)	4(1)	0	0
41–50	0	0	4(4)	1(1)	11(7)	7(4)	0	0
51–60	2(1)	0	4(3)	1(0)	3(2)	7(6)	0	0
>61	3(2)	0	2(2)	0	13(7)	3(2)	0	1(1)

Values in parentheses indicate the number of fatal infections; Pn, pneumococcal infections; other, infections with other bacteria

Table 8 *Median interval from splenectomy to development of first infection*

Indication for splenectomy	No. of patients	Percentage pneumococcal infections	Median age at splenectomy (years, months) All	Pn	Other	Median interval to infection (years, months) All	Pn	Other
Trauma	72	59·7	18, 6	21, 0	10, 6	4, 0	5, 6	3, 0
Spherocytosis	40	37·5	2, 9	6, 0	0, 8	0, 11	1, 6	0, 11
ITP	33	60·6	8, 0	22, 6	1, 5	1.0	3, 1	0, 1
Thalassaemia	28	39·3	5, 0	4, 0	6, 0	2, 0	2, 0	3, 0
Hodgkin's disease	45	46·7	18, 0	14, 0	25, 6	1, 8	1, 7	3, 0

ITP, Idiopathic thrombocytopenic purpura; all, all infections; Pn, pneumococcal infections; other, infections with bacteria other than *Pneumococcus*

Twenty-eight children with infection were reported as having had their spleen removed before their first birthday and 25 of these suffered infections before they were 2 years old[3,4,7,10–13,20,25–29,88]. Twelve infections were pure meningitis (four pneumococcal, three meningococcal, four due to *Haemophilus*, one unidentified), and only one patient with meningococcal meningitis died[3]. Twelve other infections were fatal, three pneumococcal septicaemias[4,20], one meningococcal septicaemia[29], one *E. coli* septicaemia[4], five unidentified septicaemias[3,12,18,28,88] and two unidentified pneumonias[12,26].

Relationship between age, indication for splenectomy and infecting organism. The median ages at operation and the median intervals to the development of the first infection for the principal indications for splenectomy are outlined in *Table 8*. The median age at splenectomy for trauma patients (18 years 6 months) was higher than for most other groups. The median interval to the first infection (4 years 0 months) was also prolonged. The median age at splenectomy for those suffering pneumococcal infections for the first time (21 years) was double the median age of those developing infections due to other organisms (10 years 6 months). The median interval to the development of pneumococcal infection (5 years 6 months) in trauma patients was also prolonged compared with the interval for infections caused by other organisms (3 years).

In patients with spherocytosis, the commonest indication for splenectomy in infancy, the median age at splenectomy was 2 years 9 months. The median interval to infection in this group was very short (11 months). However, the median age at splenectomy in children who developed pneumococcal infections was 6 years and these children were considerably older at operation than those who developed infections caused by other bacteria (who had a median age at splenectomy of 8 months). The interval to the onset of infection was also longer in the pneumococcal group (1 year 6 months *versus* 11 months). This trend of a longer interval to the onset of pneumococcal infection was even more marked in patients undergoing splenectomy for idiopathic thrombocytopenic purpura (22 years 6 months *versus* 1 year 5 months). Thalassaemic patients, regarded as a group prone to infection, had a low median age at splenectomy (5 years) but appeared to be equally prone to both pneumococcal infection and other infections after a similar time interval.

Severity of infection. Analysis of the individual cases of pneumococcal infection confirmed the severity of these infections after splenectomy; 78 (68 per cent) of the 114 deaths were recorded as occurring within 24 h of the onset of symptoms. A further 13 patients died within 48 h of the first symptoms. In 44 (39 per cent) patients evidence of adrenal haemorrhage was documented at autopsy. Evidence of disseminated intravascular coagulation (DIC) was present in 51 patients and only five patients with DIC survived. Only four episodes of DIC were recorded in patients with idiopathic thrombocytopenic purpura where confusion in diagnosis may arise[78–80] (L. A. Gruer and A. M. Geddes, personal communication).

Pneumococcal serotypes involved in postsplenectomy infection. Eighty-four different capsular serotypes of the pneumococcus are recognized. In this collective review details of serotypes were reported in only 35 infections out of 198 episodes of pneumococcal sepsis. A total of 14 different serotypes were isolated. Type 23 was the commonest serotype, reported in nine infections and three deaths[7,8,25,67,68,86,87]. There is no evidence that any particular serotype is responsible for pneumococcal postsplenectomy infection.

Discussion

Previously published reports on the subject of postsplenectomy infection have concluded that pneumococcal infections account for half, most of which are encountered in the first few years after operation; the highest frequency of infection is seen in young children. These conclusions underlie the widespread belief that young children after splenectomy are particularly prone to pneumococcal infection. The data presented in the present survey, when analysed collectively, confirm these findings but when scrutinized in more detail do not support the view that children and infants are more at risk from pneumococcal infection than from any other organism. However, it should be stressed that this survey has found that a substantial cohort of published reports on the subject are poorly documented with respect to patient details, age at splenectomy, and nature of infection. The available data are, therefore, suspect and their overall quality and retrospective nature preclude any definite conclusions. Nevertheless, this is the same information that has been used in the past to suggest an increased susceptibility to infection after splenectomy.

The collective review of Singer[4] is regarded as the reference text on postsplenectomy sepsis. This author calculated the risk of death from infection after splenectomy based on a mortality rate from sepsis of 0·01 per cent in the general population. On this basis he concluded that the increased risk of infection after splenectomy for trauma was 58 times, for idiopathic thrombocytopenia 143 times, for spherocytosis 223 times and for thalassaemia 1100 times. We consider that this method of risk calculation is misleading since it takes no account of the nature of the infecting organism, the age of the patient and the type of infection, all of which are important variables influencing risk of infection and death.

This study has confirmed that over half of the infections are caused by *S. pneumoniae*. This is the only organism that deserves serious consideration. Although an increased incidence of postsplenectomy infection has been reported from other encapsulated bacteria, there have been a total of only 22 case reports of *H. influenzae* infection[3,4,7–18,85,118,119,136,139] and 13 case reports of meningococcal infection[3,12,13,26,29,34,35,50,110,113] (L. D. Gruer and A. M. Geddes, personal communication). The small number of the reported cases combined with the high proportion of these infections in children, with the predominant infection being meningitis, suggests that the incidence and pattern of infection with these organisms after splenectomy is no different from that in the general population[85,142–144].

This survey has shown that the type of infection reported after splenectomy varies with the age of the patient. Children are reported to have predominantly meningitis; both *Haemophilus* and meningococcal meningitis are as important as pneumococcal meningitis in young children. In contrast, the reported infections in adults are almost entirely septicaemia or septicaemia combined with meningitis and, as a consequence, mortality rate rises.

It is important to ascertain whether these observations are specific to the asplenic state or simply reflect the natural occurrence and history of pneumococcal infections in the general population. Pneumococcal infections are among the commonest bacterial infections in man. They are a frequent cause of upper respiratory tract infection in infants and, by the age of 3 years, 65 per cent of children have had an attack of pneumococcal otitis media[145–147]. The pneumococcus is still the commonest cause of bacterial pneumonia, and pneumonia is the only infectious disease among the ten commonest causes of death in the USA[146]. Pneumococcal pneumonia predominantly affects the elderly with chronic obstructive airways disease[146]. The pneumococcus is the commonest cause of bacterial meningitis overall and the third commonest cause of meningitis in children[146–148]. Between 4 and 13 per cent of all septicaemias are caused by this organism and the incidence of pneumococcal septicaemia rises with age and is highest in the elderly[149–151]. The spectrum of pneumococcal infections after splenectomy, meningitis in children and septicaemia in adults is thus in accordance with the natural history of these infections. Pneumococcal infections are particularly common, therefore large numbers would have to be recorded after splenectomy before it would be possible to say that these were not chance events.

In people older than 15 years there have been only 29 documented cases of severe pneumococcal infection, with 20 deaths after splenectomy for trauma[44,49,66,67,90–106] (L. D. Gruer and A. M. Geddes, personal communication), eight reported cases of severe infection in those undergoing splenectomy for spherocytosis[50,66,111,113–116,132], and 11 infections after splenectomy for idiopathic thrombocytopenic purpura[14,20,49, 66,79,80,86,117] (L. D. Gruer and A. M. Geddes, personal communication). So few reports can only be interpreted as indicating that infection in adults undergoing splenectomy for benign disease is very uncommon and it is difficult to suggest that this number of reports constitutes a proven increased susceptibility to infection after splenectomy in adults.

The question of infection in children is more difficult to address. If young children are more prone to pneumococcal infection after splenectomy, it would be expected that there would be a large number of case reports of this infection. However, there have been only nine reported deaths from pneumococcal sepsis in children before their fifth birthday and only one before the age of 1 year[4,7,8,20,44,66,84]. Spherocytosis is the commonest indication for splenectomy in infants. As this disorder is not accompanied by an increased risk of sepsis, any infections after splenectomy are usually attributed to the operation[9,21–24,45,46,153]. Sixteen cases of infection are reported among children having their spleen removed for spherocytosis before their first birthday. Only three of these infections were pneumococcal: two non-fatal meningitis and one fatal septicaemia[11,20,26]. The youngest reported case of a pneumococcal infection after splenectomy for trauma is in a patient aged 6 years[89], whereas five cases of infection have been reported in children after splenectomy for trauma below this age caused by other organisms[4,13,29,30]. From this review we can find little confirmatory evidence to say that children undergoing splenectomy for benign disease become more susceptible to pneumococcal infection in preference to any other organism. Furthermore, the 22 per cent mortality rate from pneumococcal meningitis after splenectomy in those under 16 years (*Table 7*) is well within the reported mortality rate range of 13–38 per cent for this infection[141,145,148,149,154]. Thus it seems that both the incidence of and death from pneumococcal meningitis after splenectomy do not exceed the normal prevalence.

The presence of underlying disease rather than age is probably a more important factor determining the susceptibility to a pneumococcal infection after splenectomy. The highest incidence of infection was encountered after splenectomy for thalassaemia. This is a multisystem disorder with abnormal levels of immunoglobulin, alterations in complement activation, cardiopulmonary disease and haemochromatosis[16,156–161]. Thus an increased susceptibility to infection cannot be attributed to the asplenic state alone. An increased tendency to pneumococcal infection is found in chronic alcoholics and cirrhotic patients[141,146,147,152]. It is possible that extensive hepatic impairment and portal hypertension with depressed Kupffer cell phagocytic activity may be the important determinants for increased susceptibility to pneumococcal infection in thalassaemia. This would also explain the high susceptibility to infection seen in people who have their spleen removed for portal hypertension.

One feature that distinguishes postsplenectomy pneumococcal infection is the severity of the infection. Postsplenectomy septicaemia is usually described as overwhelming, with massive numbers of circulating organisms, proceeding rapidly to refractory shock and death. However, these findings can also be associated with pneumococcal infections in otherwise normal people. Untreated pneumococcal pneumonia has a mortality rate of 30 per cent, falling to about 5 per cent with antibiotic treatment. The mortality rate is doubled if pneumonia is associated with bacteraemia[146]. Pneumococcal meningitis still carries a mortality rate of up to 40 per cent in developed countries, and higher figures are reported from Africa[146–148]. The mortality rate from pneumococcal septicaemia varies from 30 to 60 per cent, depending on the presence of underlying disease, age and serotype[141,146,149,151,152]. Gransden *et al.*[149] showed that 56 of 93 deaths (60 per cent) from pneumococcal infection were in patients who were moribund on admission. Of patients admitted to intensive care, 64 per cent died, and 70 per cent of all deaths in their study occurred within 24 h of admission. Therefore, pneumococcal infection, even in those with an intact spleen, can be rapidly fatal with a clinical picture which closely simulates 'overwhelming postsplenectomy sepsis'.

It is not possible to conclude whether or not infection is increased after splenectomy. However, using the only information that is available at present, and the same information used by others in the past, we have arrived at a different conclusion. Why has there been so much published on the subject during the past 30 years? With the exception of the series of Walker[6], all the literature reports are retrospective. Perhaps there has been a disproportionate reporting of certain infections after splenectomy. In this respect, it is of interest that 110 of 150 pneumococcal infections (73 per cent) reported after splenectomy are made up of isolated case reports. In addition, 39 of 42 reports of pneumococcal infection after splenectomy for trauma in adults are also isolated case reports. It could be argued that a disproportionate reporting of pneumococcal infection has resulted in an unquestioned belief in this complication of splenectomy.

As in any medical controversy, there is a need to establish prospective longitudinal studies in patients undergoing splenectomy to resolve this matter. What is particularly important is that all patients without a spleen should not be regarded as a single group. There is a need for the assessment of the risk of specific infections as opposed to 'sepsis' in well defined clinical groups, e.g. incidence of pneumococcal meningitis in children undergoing splenectomy for spherocytosis. In this respect, estimates of risks based on collective terms such as 'overwhelming postsplenectomy sepsis' help to perpetuate the existing confusion.

References

1. Morris DH, Bullock FD. The importance of the spleen in resistance to infection. *Ann Surg* 1919; **70**: 513–21.
2. O'Donnell FJ. The value of splenectomy in Banti's disease. *Br Med J* 1929; **i**: 854.
3. King H, Shumacker HB Jr. Susceptibility to infection after splenectomy performed in infancy. *Ann Surg* 1952; **136**: 239–42.
4. Singer DB. Postsplenectomy sepsis. *Perspect Paediatr Pathol* 1973; **1**: 285–311.
5. Dickerman JD. Bacterial infection and the asplenic host: a review. *J Trauma* 1976; **16**: 662–7.
6. Walker W. Splenectomy in childhood: a review of cases in England and Wales 1960–4. *Br J Surg* 1976; **63**: 36–43.
7. Robinson TW, Sturgeon P. Post-splenectomy infections in infants and children. *Pediatrics* 1960; **25**: 941–51.
8. Smith CH, Erlandson M, Schulman I, Stern G. Hazard of severe infections in splenectomized infants and children. *Am J Med* 1957; **22**: 390–404.
9. Krueger HC, Burgert EO Jr. Hereditary spherocytosis in 100 children. *Mayo Clin Proc* 1966; **41**: 821–30.
10. Schumacher MJ. Serum immunoglobulin and transferrin levels after childhood splenectomy. *Arch Dis Child* 1970; **45**: 114–17.
11. Lowdon AGR, Walker JH, Walker W. Infection following splenectomy in childhood. *Lancet* 1962; **i**: 499–504.
12. Horan M, Colebatch JH. Relation between splenectomy and subsequent infection. A clinical study. *Arch Dis Child* 1962; **37**: 398–414.
13. Wahlby L, Domellof L. Splenectomy after blunt trauma: a retrospective study of 413 children. *Acta Chir Scand* 1981; **147**: 131–5.
14. Chaikof EL, McCabe CJ. Fatal overwhelming postsplenectomy infection. *Am J Surg* 1985; **149**: 534–9.
15. Broberger O, Gyulai F, Hirschfeldt J. Splenectomy in childhood: a clinical and immunological study of forty two children splenectomised in the years 1951–1958. *Acta Paediatr Scand* 1960; **49**: 679–89.
16. Constantoulakis M, Economopoulos P, Constantopoulos A. Infections after splenectomy. *Ann Intern Med* 1973; **78**: 780–1.
17. Donaldson SS, Glatstein E, Vosti KL. Bacterial infections in pediatric Hodgkin's disease: relationship to radiotherapy, chemotherapy and splenectomy. *Cancer* 1978; **41**: 1949–58.
18. Ein SH, Shandling B, Simpson JS *et al.* The morbidity and mortality of splenectomy in childhood. *Ann Surg* 1977; **185**: 307–9.
19. Smith CH, Erlandson MD, Stern G, Hilgartner MW. Postsplenectomy infection in Cooley's anemia: an appraisal of the problem in this and other disorders with consideration of prophylaxis. *N Engl J Med* 1962; **266**: 737–43.
20. Lowdon AGR, Stewart RHM, Walker W. Risk of serious infection following splenectomy. *Br Med J* 1966; **i**: 446–50.
21. Anderson V, Cohn J, Sorensen SF. Immunological studies in children before and after splenectomy. *Acta Paediatr Scand* 1976; **65**: 409–13.
22. Reemtsma K, Elliot RHE Jr. Splenectomy in Mediterranean anaemia: an evaluation of long-term results. *Ann Surg* 1956; **144**: 999–1007.
23. Rutkow IM. Twenty years of splenectomy for hereditary spherocytosis. *Arch Surg* 1981; **116**: 306–8.
24. Walter LE, Chaffin L. Splenectomy in infants and children. *Ann Surg* 1955; **142**: 798–803.
25. Gofstein R, Gellis SS. Splenectomy in infancy and childhood; the question of overwhelming infection following operation. *Am J Dis Child* 1956; **91**: 556–9.
26. Burman D. Congenital spherocytosis in infancy. *Arch Dis Child* 1958; **33**: 335–41.
27. Huntley CC. Infection following splenectomy in infants and children; a review of the experience at Duke Hospital in infants and children during a twenty two year period (1933–1954). *Am J Dis Child* 1958; **95**: 477–80.
28. Lucas RV Jr, Krivit W. Overwhelming infection in children following splenectomy. *J Pediatr* 1960; **57**: 185–91.
29. Wegelius R. Postsplenectomy infections. *Lancet* 1982; **i**: 1420–1 (Letter).
30. Erickson WD, Burgert EO, Lynn HB. The hazard of infection following splenectomy in children. *Am J Dis Child* 1968; **116**: 1–8.
31. Ek JI, Rayner S. An analytical study of splenectomised cases after traumatic rupture of healthy spleens. *Acta Med Scand* 1950; **137**: 417–35.
32. Wolfe JA, Sitarz AL, Von Hofe FH. Effect of splenectomy on thalassaemia. *Pediatrics* 1960; **26**: 674–8.
33. O'Neil BJ, McDonald JC. The risk of sepsis in the asplenic adult. *Ann Surg* 1981; **194**: 775–8.
34. Hancock BW, Bruce L, Ward AM, Richmond J. Changes in immune status in patients undergoing splenectomy for staging of Hodgkin's disease. *Br Med J* 1976; **i**: 313–15.
35. Thurman WG. Splenectomy and immunity. *Am J Dis Child* 1963; **105**: 138–45.
36. Breuel K, Blau HJ. Splenectomy and susceptibility to infection in childhood Hodgkin's disease. *Neoplasma* 1984; **31**: 727–30.
37. Eisenberg BL, Andreassy RJ, Haff RC, Ratner IA. Splenectomy in children. A correlative review of the indications and complications in 50 patients. *Am J Surg* 1976; **132**: 720–2.
38. Forward AD, Ashmore PG. Infection following splenectomy in infants and children. *Can J Surg* 1960; **3**: 229–33.
39. Haller JA Jr, Jones EL. Effect of splenectomy on immunity and resistance to major infections in early childhood: clinical and experimental study. *Ann Surg* 1966; **163**: 902–8.
40. Laski B, MacMillan A. Incidence of infection in children after splenectomy. *Pediatrics* 1959; **24**: 523–7.
41. McKinnon WMP, Boley SJ, Manpel J. Infection in children following splenectomy for traumatic rupture. *Am J Dis Child* 1959; **98**: 710–12.
42. Mills SD. Purpura in childhood: observations in 187 cases. *J Pediatr* 1956; **49**: 306–15.
43. Posey DL, Marks C. Overwhelming postsplenectomy sepsis in childhood. *Am J Surg* 1983; **145**: 318–21.
44. Hodam RP. The risk of splenectomy: a review of 310 cases. *Am J Surg* 1970; **119**: 709–13.
45. Schwartz SI, Bernard RP, Adams JT, Bauman AW. Splenectomy for haematological disorders. *Arch Surg* 1970; **101**: 338–47.
46. Lawrie GM, Ham JM. The surgical treatment of hereditary spherocytosis. *Surg Gynecol Obstet* 1974; **139**: 208–10.
47. Schilling RT. Hereditary spherocytosis: a study of splenectomised persons. *Semin Hematol* 1976; **13**: 169–77.
48. Bourgoult AM, Van Scoy RE, Wilkowske CJ, Zincke H, Sterioff S. Severe infection due to *Streptoccocus pneumoniae* in asplenic renal transplant patients. *Mayo Clin Proc* 1979; **54**: 123–6.
49. Askergren J Bjorkholm M. Postsplenectomy septicaemia in Hodgkin's disease and other disorders. *Acta Chir Scand* 1980; **146**: 569–75.
50. Schwartz PE, Sterioff S, Mucha P, Melton LJ, Offord MS. Postsplenectomy sepsis and mortality in adults. *JAMA* 1982; **248**: 2279–83.
51. Coker DD, Morris DM, Coleman JJ, Schimpff SC, Wiernik PH, Elias EG. Infection amongst 210 patients with surgically staged Hodgkin's disease. *Am J Med* 1983; **75**: 97–109.
52. Donaldson SS, Moore MR, Rosenberg SA, Vosti KL. Characterisation of postsplenectomy bacteremia among patients with and without lymphoma. *N Engl J Med* 1972; **287**: 69–71.
53. Carlstedt A, Tholin B. Infectious complications of splenectomy. *Acta Chir Scand* 1984; **150**: 607–10.
54. Chilcote RR, Baehner RL, Hammond D. Septicemia and meningitis in children splenectomized for Hodgkin's disease. *N Engl J Med* 1976; **295**: 798–800.
55. Desser RK, Ultmann JE. Risk of severe infection in patients with Hodgkin's disease or lymphoma after diagnostic laparotomy and splenectomy. *Ann Intern Med* 1972; **77**: 143–6.
56. Eraklis AJ, Kevy SV, Diamond LK, Gross RE. Hazard of overwhelming infection after splenectomy in childhood. *N Engl J Med* 1967; **276**: 1225–9.
57. Eraklis AJ, Filler RM. Splenectomy in childhood. A review of 1413 cases. *J Pediatr Surg* 1972; **7**: 382–8.
58. Konigswieser H. Incidence of serious infections after splenectomy in childhood. *Prog Pediatr Surg* 1985; **18**: 173–81.
59. McEnery PT, Flanagan J. Fulminant sepsis in splenectomized children with renal allografts. *Transplantation* 1977; **24**: 154–5.
60. Malangoni MA, Dillon LD, Klamer TW, Condon PE. Factors influencing the risk of early and late serious infection in adults after splenectomy for trauma. *Surgery* 1984; **96**: 775–83.
61. Pedersen FK. Postsplenectomy infections in Danish children splenectomized 1969–1978. *Acta Paediatr Scand* 1983; **72**: 589–95.
62. Robinette CD, Fraumeni JF. Splenectomy and subsequent

mortality in veterans of 1939–45 war. *Lancet* 1977; **ii**: 127–9.

63. Schimpff SC, O'Connell MJ, Greene WH, Wiernik PH. Infections in 92 splenectomized patients with Hodgkin's disease. *Am J Med* 1975; **59**: 695–701.
64. Edwards LD, Digioia R. Infections in splenectomised patients. A study in 131 patients. *Scand J Infect Dis* 1976; **8**: 255–61.
65. Standage BA, Goss JC. Outcome and sepsis after splenectomy in adults. *Am J Surg* 1982; **143**: 545–8.
66. Whitaker AN. Infection and the spleen: association between hyposplenism, pneumococcal sepsis and disseminated intravascular coagulation. *Med J Aust* 1969; **1**: 1213–19.
67. Gopal V, Bisno AL. Fulminant pneumococcal infections in 'normal' asplenic hosts. *Arch Intern Med* 1977; **137**: 1526–30.
68. Greene JR, Polk OD, Castro O. Fulminant pneumococcal sepsis in an adult with sickle-cell anaemia. *N Engl J Med* 1984; **311**: 674 (Letter).
69. Bensinger TA, Keller AR, Merrell LF, O'Leary DS. Thorotrast-induced reticuloendothelial blockade in man: clinical equivalent of the experimental model associated with patent pneumococcal septicaemia. *Am J Med* 1971; **51**: 663–8.
70. Bisno AL, Freeman JC. The syndrome of asplenia, pneumococcal sepsis and disseminated intravascular coagulation. *Ann Intern Med* 1970; **72**: 389–93.
71. Chilcote RR, Dampier C. Overwhelming pneumococcal septicaemia in a patient with HbSC disease and splenic dysfunction. *J Pediatr* 1984; **104**: 734–6.
72. Grant MD, Horowitz HI, Lorian V, Brodman HR. Waterhouse–Friderichson syndrome induced by pneumococcemic shock. *JAMA* 1970; **212**: 1373–4.
73. Hatch JP, Sibbald WJ, Austin TW. Overwhelming pneumococcal infection in a hyposplenic adult. *Can Med Assoc J* 1983; **129**: 851–4.
74. Kabins SA, Lerner C. Fulminant pneumococcemia and sickle cell anaemia. *JAMA* 1970; **211**: 467–71.
75. Myerson RM, Koelle WA. Congenital absence of the spleen in an adult: report of a case associated with recurrent Waterhouse–Friderichsen syndrome. *N Engl J Med* 1956; **254**: 1131–2.
76. Parr LJA, Shipton EA, Holland EH. A fatal case of Still's disease associated with Waterhouse–Friderichsen syndrome due to pneumococcal septicaemia. *Med J Aust* 1953; **1**: 300–5.
77. Torres J, Bisno AL. Hyposlenism and pneumococcemia. Visualization of *Diplococcus pneumoniae* in the peripheral blood smear. *Am J Med* 1973; **55**: 851–5.
78. McCracken GH Jr, Dickerman JD. Septicaemia and disseminated intravascular coagulation: occurrence in four asplenic children. *Am J Dis Child* 1969; **118**: 431–4.
79. Irsigler GB, Lubin A. Untitled letter to the editor. *Ann Intern Med* 1970; **73**: 140–1.
80. Kingston ME, MacKenzie CR. The syndrome of pneumococcaemia, disseminated intravascular coagulation and asplenia. *Can Med Assoc J* 1979; **121**: 57–61.
81. Butler T, Weaver RE, Ramani TKV *et al.* Unidentified Gram-negative rod infection: a new disease in man. *Ann Intern Med* 1977; **86**: 1–5.
82. Archer GL, Coleman PH, Cole RM, Duma RJ, Johnston CL. Human infection from an unidentified erythrocyte-associated bacterium. *N Engl J Med* 1979; **301**: 897–900.
83. Findling JW, Pohlmann GP, Rose HD. Fulminant Gram-negative bacillemia (DF-2) following a dog bite in an asplenic woman. *Am J Med* 1980; **68**: 154–6.
84. Evans DIK. Fatal postsplenectomy sepsis despite prophylaxis with penicillin and pneumococcal vaccine. *Lancet* 1984; **i**: 1124 (Letter).
85. Eykyn SJ, Thomas RD, Phillips I. *Haemophilus influenzae* meningitis in adults. *Br Med J* 1974; **ii**: 463–5.
86. Schlaeffer F, Rosenheck S, Baumgarten-Kleinen A, Crieff Z, Alkan M. Pneumococcal infections among immunised and splenectomised patients in Israel. *J Infect* 1985; **10**: 38–42.
87. Giebink GS, Schiffmann G, Krivit W, Quie PG. Vaccine-type pneumococcal pneumonia. Occurrence after vaccination in an asplenic patient. *JAMA* 1979; **241**: 2736–7.
88. Gruber SB, Redner B, Kogut B. Congenital idiopathic thrombocytopenic purpura in a premature infant with splenectomy. *NY State J Med* 1951; **51**: 649–50.
89. Appelbaum PC, Shaikh BS, Widome MD, Gordon RA, Austrian R. Fatal pneumococcal bacteremia in a vaccinated, splenectomized child. *N Engl J Med* 1979; **300**: 203–4.
90. Alestig K, Norrby R. Fatal pneumococcal septicaemia in a young asplenic man. *Acta Chir Scand* 1979; **145**: 273–5.
91. Andersson T, Julander I, Lundbergh P, Morfeldt-Manson L. Sepsis och purulent meningit hos splenektomerade patienter. *Lakartidningen* 1979; **76**: 4475–8.
92. Cairns FY, Say PJ. Fulminant pneumococcal septicaemia in an adult following splenectomy: case report. *NZ Med J* 1979; **89**: 85–6.
93. Grinblat J, Gilboa Y. Overwhelming pneumococcal sepsis 25 years after splenectomy. *Am J Med Sci* 1975; **270**: 523–4.
94. Haque AU, Min KW, From P, Song J. Postsplenectomy pneumococcaemia in adults. *Arch Pathol Lab Med* 1980; **104**: 258–60.
95. Kartz SC, Thompson RE, Depenbusch FL, Hart GB. Hyperbaric oxygen treatment of gangrene in pneumococcemia. *JAMA* 1971; **217**: 962–3.
96. Ludmerer KM, Kissane JM. Clinicopathological conference: septic shock in a young splenectomized man. *Am J Med* 1983; **74**: 129–43.
97. Moore GE, Stevens RE, Moore EE, Aragon GE. Failure of splenic implants to protect against fatal postsplenectomy infection. *Am J Surg* 1983; **146**: 413–14.
98. Oakes DD, Charters AC. Changing concepts in the management of splenic trauma. *Surg Gynecol Obstet* 1981; **153**: 181–5.
99. Ramsey LE, Bouskill KC. Fatal pneumococcal meningitis in adults following splenectomy: two case reports and review of the literature. *J R Nav Med Serv* 1973; **59**: 102–14.
100. Reay DI, Nakonechny D. Sudden death and sepsis after splenectomy. *J Forensic Sci* 1979; **24**: 757–61.
101. Reed WP, Chick TW, Jutila K, Butler C, Goldblum S. Pulmonary leukostasis in fatal human pneumococcal bacteremia without pneumonia. *Am Rev Respir Dis* 1984; **130**: 1184–7.
102. Rice HM, James PD. Ectopic splenic tissue failed to prevent pneumococcal septicaemia after splenectomy for trauma. *Lancet* 1980; **i**: 565–6.
103. Sculley RE, Galdabini JJ, McNeely BU. Case records of the Massachusetts General Hospital; weekly clinico-pathological exercises. Case 36-1975. *N Engl J Med* 1975; **293**: 547–53.
104. Sher R, Block CS, Gomperts ED. Overwhelming pneumococcaemia 17 years after splenectomy: a case report. *S Afr Med J* 1979; **55**: 643–6.
105. Stossel TP, Levy R. Intravascular coagulation associated with pneumococcal bacteremia and symmetrical peripheral gangrene. *Arch Intern Med* 1970; **125**: 876–8.
106. Brigden ML. Post-splenectomy sepsis syndrome: how to identify and manage patients at risk. *Postgrad Med* 1985; **77**: 215–26.
107. Coler RS. Postsplenectomy sepsis. A review of the literature and two new cases. *Northwest Med* 1963; **62**: 865–70.
108. Finnegan OC, Hawkey PM. Overwhelming post-splenectomy infection with group B streptococcus. *Postgrad Med J* 1981; **57**: 202–3.
109. Goldstein DA, Craig JP, Sutton AL. Fatal cholera-like diarrhea with Waterhouse–Friderichson syndrome, sickle-cell trait, and hyposplenism. *NY State J Med* 1977; **77**: 1936–40.
110. Holmes FF, Weyandt T, Glazier J, Cuppage FE, Moral LA, Lindsey WJ. Fulminant meningococcemia after splenectomy. *JAMA* 1981; **246**: 1119–20.
111. Reis TC, Clark C, Burris O, O'Rouke S, Cowan V, Daniels L. Postsplenectomy sepsis. *N Engl J Med* 1983; **309**: 926 (Letter).
112. Rose FB, Camp CJ, Chisdak M. Disseminated histoplasmosis and asplenia. *Ann Intern Med* 1982; **96**: 790.
113. Evans DIK. Postsplenectomy sepsis 10 years or more after operation. *J Clin Pathol* 1985; **38**: 309–11.
114. Karatsas NB. Fatal pneumococcal septicaemia after splenectomy. *Br Med J* 1966; **ii**: 1500–1.
115. Roberts GT, Roberts JT. Postsplenectomy sepsis due to influenzal viremia and pneumococcemia. *Can Med Assoc J* 1976; **115**: 435–7.
116. Scully RE, Mark EJ, McNeely BU. Case records of the Massachusetts General Hospital; weekly clinico-pathological exercises. Case 20-1983. Hyperthermia of acute onset in an asplenic man. *N Engl J Med* 1983; **308**: 1212–18.
117. Brivet F, Herer B, Freman A, Durmont J, Tchernia G. Fatal postsplenectomy pneumococcal sepsis despite pneumococcal vaccine and penicillin prophylaxis. *Lancet* 1984; **ii**: 356–7 (Letter).
118. Kyong K, Reines HD. *Haemophilus influenzae* sepsis in a splenectomized child. *N Engl J Med* 1979; **301**: 271.
119. Ravry M, Maldonado N, Velez-Garcia E, Montalvo J, Santiago PJ. Serious infections after splenectomy for the staging of Hodgkin's disease. *Ann Intern Med* 1972; **77**: 11–14.

120. Balfanz JR, Nesbit ME Jr, Jarvis C, Krivit W. Overwhelming sepsis following splenectomy for trauma. *J Pediatr* 1976; **88**: 458–60.
121. Coonrod JD, Leach RP. Antigenemia and fulminant pneumococcemia. *Ann Intern Med* 1976; **84**: 561–3.
122. Curti AJ, Lin JH, Szabo K. Overwhelming post-splenectomy infection with *Plesimonas shigelloides* in a patient cured of Hodgkin's disease: a case report. *Am J Clin Pathol* 1985; **83**: 522–4.
123. Daily MO, Coleman CN, Kaplan HS. Radiation-induced splenic atrophy in patients with Hodgkin's disease and non-Hodgkin lymphoma. *N Engl J Med* 1980; **302**: 215–17.
124. Farber S, Craig JM. Clinico-pathological conference. *J Pediatr* 1957; **51**: 716–25.
125. Hanawa M, Kobayashi H, Oishi M, Fujisawa H, Matasuoka M. A case of Waterhouse–Friderichsen syndrome after splenectomy. *Jpn J Haematol* 1978; **20**: 308–13.
126. Huntley CC, Dees SC. Eczema associated with thrombocytopenic purpura and purulent otitis media. *Pediatrics* 1957; **19**: 351–61.
127. Jindrich J. Splenectomy and sudden death. *J Forensic Sci* 1977; **22**: 610–13.
128. Lodewick PA. Fatal pneumococcal septicaemia with disseminated intravascular coagulation following splenectomy. *J Med Soc NY* 1975; **72**: 730–1.
129. Maron BJ, Maloney JR. Septicaemia following traumatic or incidental splenectomy. *Johns Hopkins Med J* 1972; **130**: 266–8.
130. McCulloch DK, Parker AG. Overwhelming postsplenectomy infection caused by *Streptococcus milleri*. *J Infect* 1979; **1**: 379–81.
131. Murphy JW, Mitchell WA. Congenital absence of the spleen. *Pediatrics* 1957; **20**: 253–6.
132. Ratnoff OD, Nehehay WG. Multiple coagulative defects in a patient with Waterhouse–Friderichson syndrome. *Ann Intern Med* 1962; **56**: 627–32.
133. Recant L, Lacy P. Clinicopathological conference: an acute terminal episode with fever, malaise, vomiting, diarrhoea, and acrocyanosis in a patient with rheumatoid arthritis. *Am J Med* 1964; **37**: 294–305.
134. Rosner F, Ritz NB. The defibrination syndrome. *Arch Intern Med* 1966; **117**: 17–24.
135. Rytel MW, Dee TH, Ferstenfeld JE, Hensley GT. Possible pathogenic role of capsular antigens in fulminant pneumococcal disease with disseminated intravascular coagulation. *Am J Med* 1974; **57**: 889–96.
136. Schroter GPJ, West JC, Weil R III. Acute bacteremia in asplenic renal transplant patients. *JAMA* 1977; **237**: 2207–8.
137. Simpkiss MJ, Cathie IA. Splenectomy for idiopathic thrombocytopenic purpura. *Great Ormond St J* 1954; **7**: 9–14.
138. Stiver G, Kendrick M, Sharrar R, Eickhoff T. Bacterial risk in staging splenectomy. *Ann Intern Med* 1972; **76**: 670.
139. Weitzman S, Aisenberg A. Fulminant sepsis after successful treatment of Hodgkin's disease. *Am J Med* 1977; **62**: 47–50.
140. Wenk RE, Dutta D. Hyposplenic coagulopathic, cryptogenic pneumococcemia. *Am J Clin Pathol* 1975; **64**: 405–9.
141. Lamothe F, Delage G, Laverdiere M, Saint-Antoine P. Serogroups and serotypes of pneumococci in Montreal: correlations with age, outcome and indications for vaccination. *Can Med Assoc J* 1984; **130**: 737–40.
142. Nixon DW, Aisenberg AC. Fatal *Haemophilus influenzae* sepsis in an asymptomatic splenectomized Hodgkin's disease patient. *Ann Intern Med* 1972; **77**: 69–71.
143. McGowan JE, Klein JO, Bratton L, Barnes MW, Finland M. Meningitis and bacteremia due to *Haemophilus influenzae*: occurrence and mortality at Boston City Hospital in 12 selected years, 1935–1972. *J Infect Dis* 1974; **130**: 119–24.
144. Loggie BW, Hinchey EJ. Does splenectomy predispose to meningococcal sepsis? An experimental study and clinical review. *J Pediatr Surg* 1986; **21**: 326–30.
145. Gray BM, Converse GM III, Dillon HC Jr. Serotypes of *Streptococcus pneumoniae* causing disease. *J Infect Dis* 1979; **140**: 979–83.
146. Willet HP. *Streptococcus pneumoniae*. In: Joklik WK, Willet HP, Amos DB, eds. *Zinsser Microbiology*, 18th edn. Norwalk, Connecticut: Appleton-Century-Crofts, 1984: 477–89.
147. Colman G, Hallas G. Systemic disease caused by pneumococci. *J Infect* 1983; **7**: 248–55.
148. Baird DR, Whittle HC, Greenwood BM. Mortality from pneumococcal meningitis. *Lancet* 1976; **ii**: 1344–6.
149. Gransden WR, Eykyn SJ, Phillips I. Pneumococcal bacteraemia: 325 episodes diagnosed at St. Thomas's Hospital. *Br Med J* 1985; **290**: 505–8.
150. Bruan B, Sloth K, Bentzon MW, Frederiksen W. A study of bacteraemia in Denmark from 1977–78. *Acta Pathol Microbiol Immunol Scand* [*B*]. 1982; **90**: 309–17.
151. Ruben FC, Norden CW, Korica Y. Pneumococcal bacteremia at a Medical/Surgical hospital for adults between 1975 and 1980. *Am J Med* 1984; **77**: 1091–4.
152. Lockley MR, Wise R. Pneumococcal infections. *Br Med J* 1984; **288**: 1179–80 (Editorial).
153. Lopez-Karpovitch X, Ortiz A, Padros-Semorile MR. Lymphocyte subpopulations and serum immunoglobulins in splenectomized patients with hereditary spherocytosis. *Rev Invest Clin* 1984; **36**: 17–20.
154. Pedersen FK, Henrichsen J. Pneumococcal meningitis and bacteraemia in Danish children 1969–79. Serotypes, incidence and outcome. *Acta Pathol Microbiol Immunol Scand* [*B*] 1983; **91**: 129–34.
155. Prober CG, Frayha H, Klein M, Schiffman G. Immunological responses of children to serious infections with *Streptococcus pneumoniae*. *J Infect Dis* 1983; **148**: 427–35.
156. Constantoulakis M, Trichopoulos D, Avgoustaki O, Economidou J. Serum immunoglobulin concentrations before and after splenectomy in patients with homozygous beta-thalassaemia. *J Clin Pathol* 1978; **31**: 546–50.
157. Seitanidis B, Mihas A, Angeloulos B. Serum immunoglobulins in beta-thalassaemia after splenectomy. *Acta Haematol* 1971; **46**: 267–70.
158. Neri A, Brugiatelli M, Iacopino P, Callea V, Ronco F. Natural killer cell activity and T subpopulations in thalassaemia major. *Acta Haematol* 1984; **71**: 263–9.
159. Nishiya K, Gupta S, De Sousa M. Differential inhibitory effect of iron on E, EA and EAC rosette formation. *Cell Immunol* 1979; **46**: 405–8.
160. Koren A, Haasz R, Tiatler A, Katzuni E. Serum immunoglobulin levels in children after a splenectomy. A prospective study. *Am J Dis Child* 1984; **138**: 53–5.
161. Khalifa AS, Kattah SA, Maged Z, Sabry F, Mohammed HA. Immunoglobulin levels, opsonic activity and phagocytic power in Egyptian thalassaemic children. *Acta Hematol* 1983; **69**: 136–9.

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Clinical and functional outcome after restorative proctocolectomy

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Restorative proctocolectomy and ileal pouch–anal anastomosis (IPAA) has been carried out on 88 patients since 1982. Three different pouch designs (J, S and W) were used. Ten pouches had to be removed. Detailed analysis was performed on 61 patients (J = 23, S = 15, W = 23) whose pouches had been functioning for at least 6 months. There was no significant difference in surgical complications before or after ileostomy closure between pouch designs but the hospital stay was greater after construction of an S pouch (P < 0·05)*. There were no significant differences in stool frequency, degree of continence or urgency between the three types. Twelve patients with J pouches required antidiarrhoeal medication compared with only one with S and five with W pouches. Only seven patients with S pouches could defaecate spontaneously compared with 22 with W pouches and all patients with J pouches* (P < 0·001)*. Twenty-five of 29 patients who had preservation of the anal transition zone had perfect continence compared with 23 of 32 with a mucosal proctectomy* (P = n.s.)*. Pouchitis occurred in 13 patients, all of whom had ulcerative colitis. In a subgroup of 23 patients, pouch evacuation was assessed scintigraphically. There was no difference in pouch capacity or total volume evacuated, but spontaneous evacuation was better in J and W pouches compared with S pouches.*

Restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) is established management for ulcerative colitis and familial adenomatous polyposis[1,2] and has been used in some functional bowel disorders such as idiopathic constipation[3,4]. Four ileal pouch designs have evolved: the triple-loop S pouch[5], the two-loop J pouch[6], the lateral isoperistaltic pouch[7] which is rarely used, and the four-loop W pouch[8]. Few studies have compared the functional results of the different pouch designs and their results are often conflicting[8–11].

In Oxford, IPAA has been performed since 1982 and J, S and W pouch designs have been used. This study compared the functional outcome of these three pouch types clinically and by using a scintigraphic method to measure pouch capacity and emptying characteristics.

Patients and methods

Clinical assessment

Restorative proctocolectomy with a pelvic ileal reservoir was performed on 88 patients between August 1982 and May 1990. Sixty-one patients with pouches functioning for at least 6 months by 1 May 1990 were included for detailed assessment. Details of the previous medical history, indication for and details of pouch surgery, length of hospital stay and complications were obtained. All patients were seen regularly and had completed a detailed questionnaire on pouch function which included daytime and nocturnal frequency of defaecation, urgency, continence, mode of pouch evacuation, use of antidiarrhoeal therapy, and sexual and urinary problems. Patients were asked to compare the result of their operation with the temporary ileostomy which they had all experienced.

Continence was considered total if there was no leakage of mucus or faeces, minor incontinence if there was minimal leakage of mucus or faeces but not sufficient to require regular wearing of a pad (usually occurring at night only), and troublesome incontinence when there was faecal leakage necessitating the use of a pad both day and night[8]. The mean number of evacuations during day and night were recorded for each patient. Those patients who evacuated their pouch at night less frequently than once a week were considered to have no nocturnal defaecation. Urgency was defined as an inability to defer defaecation for at least 30 min[9]. Pouchitis was defined as the occurrence of diarrhoea, usually with bleeding, with pouch inflammation on sigmoidoscopy in the absence of specific pathogenic organisms in the pouch stool[12–15]. The diagnosis was confirmed histologically[12,16].

Scintigraphic assessment

Maximum tolerated pouch capacity (MTC) and pouch evacuation were assessed in 23 (J = 6, S = 10, W = 7) patients with pelvic ileal pouches (17 men; median age 32 years, range 22–56 years). The pouches had been functioning for at least 1 year (median 27 months, range 13–72 months). All 23 patients had previously had ulcerative colitis, and seven of them had pouchitis at the time of the study. None of the patients had an anastomotic stricture.

The scintigraphic technique used was a modification of that described and validated by O'Connell *et al.*[17]. The patients were fasted for 8 h before the study and all medication was withheld. In patients with pouchitis the study was performed within 24–48 h of presentation. The patient was asked to empty the pouch as completely as possible and residual faeces were drained via a sigmoidoscope immediately before the study.

An artificial stool was prepared by suspending 7·5 per cent aluminium magnesium silicate (Veegum, RT Vanderbilt Company Incorporated, Norwalk, Connecticut, USA) by weight in water at 37°C. The consistency of the 7·5 per cent suspension was closest to the semisolid consistency of pouch stool[17]. The suspension was labelled by adding 10 MBq of a very poorly absorbable marker, ^{99m}Tc-labelled DTPA (diethylene triaminepenta-acetate), during thorough agitation. *In vitro* studies showed more than 85 per cent of the radioactivity to be fixed to the silicate gel, and that the variation in activity was less than 5 per cent throughout the suspension. The artificial stool was instilled into the pouch via a transanal tube with the patient lying in the left lateral position with the hips fully flexed until the patient developed a constant feeling of impending defaecation, which was taken as the MTC. The patient was asked to retain the suspension until the dynamic study. The patient was imaged using an IGE400T γ camera (International General Electric, Slough, UK) interfaced with an NUD512+ computer system (Nuclear Diagnostic, Dartford, UK). Initial pre-evacuation 3-min static posterior and right lateral images of the pelvis were obtained with the patient seated on a commode. After commencement of a posterior pelvis dynamic acquisition at one frame per second for 4 min, the patient was asked to defaecate without moving while sitting on the commode (spontaneous evacuation). This acquisition was terminated early if the patient could not evacuate the

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pouch spontaneously at all or had emptied as much as possible. Assisted evacuation was used by all patients and consisted of manual abdominal wall pressure or a change of position not usually used in spontaneous evacuation. Eight of ten patients with S pouches used a catheter. After assisted evacuation ('total' evacuation), postevacuation 3-min static posterior and right lateral images of the pelvis were obtained with the patient again sitting on the commode. Finally, a 50-ml sample of the suspension was measured on the γ camera and the counts per millilitre were computed. MTC was calculated as:

$$\mathrm{MTC} = \frac{\text{Total counts in the pre-evacuation pouch scan}}{\text{Counts per ml of suspension}}$$

When calculating MTC any radioactivity which had refluxed into the terminal ileum was not counted. Emptying curves for the dynamic phase were derived and pouch evacuation was calculated by counting the activity in the pouch images obtained before and after evacuation (both spontaneous and total) (*Figure 1*). Spontaneous and total pouch evacuation were expressed as a percentage of the dose of radioactivity instilled. Percentage evacuation was correlated to clinical pouch function.

Statistical analysis

Grouped data were expressed as median and range. Differences between measurements were assessed by the Mann–Whitney *U* test, and the differences between proportions were assessed by Fisher's exact test. The significance of correlation was determined by the Spearman rank correlation test. Statistical significance was taken as $P < 0.05$.

Results

Clinical assessment

There were no operative deaths. Ten (J = 4, S = 2, W = 4) of the 88 pouches have been removed: three for pelvic sepsis, three for pouch ischaemia, two because of Crohn's disease unsuspected at the time of surgery, one for severe pouchitis resistant to medical treatment, and one for unacceptable pouch function. Six of these pouches were excised before the diverting ileostomy was closed and the other four were excised within 3 years of ileostomy closure, giving a failure rate of 11 per cent.

Detailed analysis was performed on 61 patients whose pouches had been functioning for at least 6 months. Details of the patients assessed are given in *Table 1*. Details of surgery are given in *Table 2*.

Sixteen of the 61 patients (26 per cent) needed reoperation: six for intestinal obstruction, three to repair vaginal fistulae, three because of sepsis, and one each for pouch ischaemia (to refashion the pouch), intra-abdominal haemorrhage, pouch–anal anastomotic dehiscence, and refashioning of the diverting ileostomy after severe skin excoriation.

The surgical complications before and after ileostomy closure are given in *Table 3*. Just over half of the 61 patients (51 per cent) had at least one surgical complication. Small intestinal obstruction due to adhesions (25 per cent) (40 per cent of these patients required laparotomy), sepsis (20 per cent), pouch–anal anastomotic stricture (16 per cent), fistula formation (10 per cent) and haemorrhage (7 per cent) were the most frequent.

Table 4 gives the functional results of the three pouch types. None of the patients had pouchitis at the time of the final

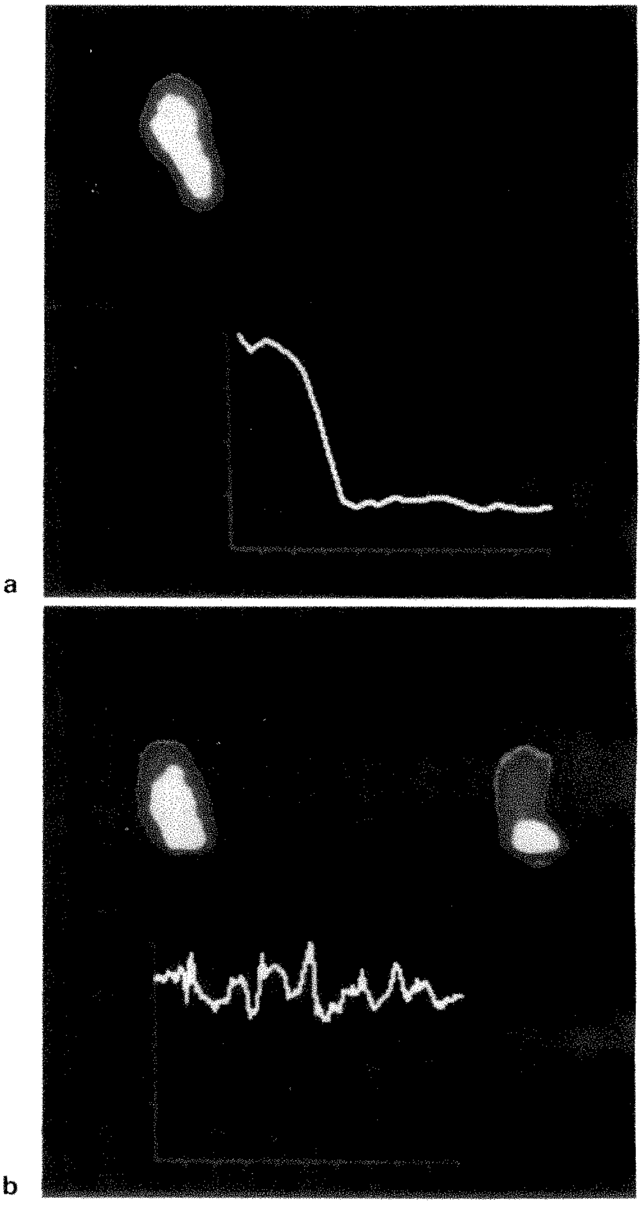

Figure 1 *Images before and after evacuation, with emptying curves for the dynamic phase of a J pouch that has emptied well* **a** *and an S pouch that has hardly emptied at all* **b**

Table 1 *Patient details*

	J pouch (*n* = 23)	S pouch (*n* = 15)	W pouch (*n* = 23)	Total (*n* = 61)
Median age (years)	35 (21–56)	31 (20–48)	30 (19–54)	31 (19–56)
M:F	14:9	13:2	16:7	43:18
Median time from ileostomy closure (months)	18 (6–76)	39* (23–82)	19 (6–46)	27 (6–82)
Diagnosis				
Ulcerative colitis	21	12	23	56
Familial adenomatous polyposis	1	3	0	4
Constipation	1	0	0	1
Ulcerative colitis				
Acute	13	7	11	31
Chronic	6	4	10	20
Dysplasia	2	1	2	5

Values in parentheses are ranges; * $P < 0.001$ compared with W pouches

Table 2 *Surgery*

	J pouch ($n=23$)	S pouch ($n=15$)	W pouch ($n=23$)	Total ($n=61$)
Two-stage/three-stage procedure	10/13	5/10	8/15	23/38
Median hospital stay after pouch formation (days)	11 (8–30)	14* (10–26)	11 (6–20)	
Median hospital stay after ileostomy closure (days)	8 (4–24)	8 (5–16)	8 (3–19)	
No. of patients needing reoperation	5	4	7	16
Pouch–anal anastomosis				
Stapled	12	0†	14	26
Handsewn	11	15	9	35
Anal transition zone preserved	12	0†	17	29

Values in parentheses are ranges; * $P<0.05$; † $P<0.005$ compared with J or W pouches

Table 3 *Surgical complications before and after ileostomy closure*

	No. of patients with complications							
	J pouch ($n=23$)		S pouch ($n=15$)		W pouch ($n=23$)		Total ($n=61$)	
	Before	After	Before	After	Before	After	Before	After
Sepsis	2	1	4	2	3	0	9	3
Pelvic	2	0	3	1	1	0	6	1
Abdominal	0	0	0	0	1	0	1	1
Wound	0	1	1	1	1	0	2	2
Intestinal obstruction	0	5	3	3	2	2	5	10
Conservative	0	3	2	3	0	1	2	7
Laparotomy	0	2	1	0	2	1	3	3
Pouch–anal anastomotic dehiscence	2	0	0	0	1	1	3	1
Pouch–anal stricture needing dilatation	0	4	0	4	0	2	0	10
Haemorrhage	3*	0	0	0	1	0	4	0
Fistulae	1†	1‡	0	2§	2†	0	3	3
Urinary retention	1	0	0	0	0	0	1	0
Pouch ischaemia	0	0	1	0	0	0	1	0
Skin excoriation	1	0	0	0	0	0	1	0
Deep vein thrombosis¶	0	1	0	0	0	0	1	0
No. of patients without complications	17	11	10	6	15	13	42	30

* One haemorrhage from a staple pouch suture line, two from pelvic bleeding; † anovaginal fistula; ‡ ileovesical fistula; § pouch–vaginal fistula; ¶ patients wore antiembolus stockings and had low-dose subcutaneous heparin prophylaxis until mobile. There was no significant difference in the incidence of individual complications or proportion of patients without complication across the three groups

functional assessment. The seven patients with S pouches who could empty their pouches spontaneously had pouches with short (2 cm) efferent segments, but two of the eight patients who used a catheter also had 2 cm efferent segments and six had long (5 cm) efferent segments. The patients who needed to catheterize their pouches did not consider it a major disadvantage. Three (5 per cent) patients (two men, one woman) had sexual problems. The woman had a vaginal discharge which inhibited sexual activity and both men had partial erectile impotence after surgery. Of the 61 patients, 32 had a complete mucosal proctectomy. Twenty-five (86 per cent) of the patients who had the anal transition zone preserved had perfect continence compared with 23 (72 per cent) of the patients who had a mucosal proctectomy. This difference did not reach statistical significance.

Pouchitis

Pouchitis occurred in 13 of 61 patients (21 per cent). In one patient pouchitis was continuous and resistant to all forms of medical treatment. The pouch was excised and for the sake of completeness details have been added to the data on functioning pouches to make 62 patients in all, with an incidence of pouchitis of 21 per cent. There was no significant difference in the incidence of pouchitis between the three pouch types (J = 6/23, S = 5/15, W = 2/24); five of the 13 (38 per cent) had only one episode of pouchitis. Pouchitis responded to metronidazole alone in seven (54 per cent) patients, while local and/or systemic steroids were required in four, and 5-aminosalicylic acid derivatives were required in three patients.

Pouchitis occurred only in patients who had previously had ulcerative colitis. Nine of the 13 (69 per cent) patients who subsequently developed pouchitis had one or more extraintestinal manifestations of ulcerative colitis before IPAA. Of the 44 patients with ulcerative colitis who did not subsequently develop pouchitis, only eight (18 per cent) had extraintestinal manifestations before IPAA. This difference was highly significant ($P<0.005$). These extraintestinal manifestations before IPAA included aphthous stomatitis ($n=8$), peripheral arthritis ($n=4$), sacroiliitis ($n=1$), ankylosing spondylitis ($n=1$), iritis ($n=5$) and pyoderma gangrenosum ($n=2$). Three patients with pouchitis subsequently continued to develop extraintestinal manifestations (arthritis and iritis, ankylosing spondylitis, and aphthous stomatitis). Other autoimmune diseases (primary sclerosing cholangitis and warm antibody autoimmune haemolytic anaemia) were present in two of the 13 patients who developed pouchitis. They were not seen in any of the 44 patients who did not develop pouchitis ($P = 0{\cdot}05$). Pouchitis developed in ten of the 46 (22 per cent) patients who had total ulcerative colitis at the time of colectomy and in three of 11 (27 per cent) patients who had distal or left-sided disease (inflammation not extending proximal to the splenic flexure). This difference was not statistically significant.

Scintigraphic assessment

The times of follow-up, approximate length of bowel used to construct the pouch, number of patients with pouchitis, MTC and emptying characteristics for each pouch design are given in *Table 5*. Despite the fact that the length of bowel used to construct the pouches was also significantly different between the three groups, MTC at least 1 year after ileostomy closure was not. As expected, spontaneous evacuation in J and W pouches was significantly better than in S pouches, but total emptying was not significantly different between the three groups of patients. Patients with pouchitis had a higher evacuation frequency and a higher incidence of incontinence than those without pouchitis (median (range) frequency 7 (6–12) *versus* 4 (2–9), $P < 0{\cdot}005$; incontinence 71 *versus* 35 per cent, $P =$ n.s.). There was no significant difference in MTC or evacuation between patients with and without pouchitis. No difference was seen in the percentage total evacuation between patients who had urgency ($n = 6$ (five with pouchitis), 46 per cent (range 5–72 per cent)) and those who did not ($n = 17$ (two with pouchitis), 48 per cent (range 2–84 per cent)).

Table 4 *Functional results*

	J pouch ($n = 23$)	S pouch ($n = 15$)	W pouch ($n = 23$)	Total ($n = 61$)
Median daytime bowel frequency	5 (3–8)	4 (2–6)	4 (2–7)	
Median nocturnal bowel frequency	0 (0–1)	0 (0–1)	0 (0–2)	
Continence				
Total continence	18	11	19	48
Minor continence	4	4	2	10
Troublesome incontinence	1	0	2	3
Urgency	1	0	1	2
Pouch evacuation				
Spontaneous	23	7*	22	52
Catheter only	0	5	1	6
Catheter sometimes	0	3	0	3
No. using anti-diarrhoeals	12	1	5	18
Sexual problems	2	1	0	3
Very happy with result	20	14	21	55

Values in parentheses are ranges; * $P < 0{\cdot}001$ compared with J or W pouches; † $P < 0{\cdot}05$ compared with S or W pouches

Discussion

IPAA has a low operative mortality rate. In a symposium where the surgical complications of 759 patients from various centres undergoing IPAA were reviewed, the operative mortality rate was found to be 0·14 per cent[18]. There were no operative or late deaths in this series. The pouch had to be excised in 11 per cent of patients and this compares with previously reported failure rates of from 6 per cent[8,19] to 13 per cent[20,21]. IPAA has a considerable morbidity rate, with an overall complication rate varying between 30 and 51 per cent[8,9,21–23]; ours was 51 per cent. The major causes of surgical morbidity were similar to those found in many other series[1,8,18–20,22,24]. The overall reoperation rate (26 per cent) was higher than that reported by others (12–14 per cent)[25–27] but the reoperation rate for patients with intestinal obstruction (40 per cent) is similar to that in other series (37–50 per cent)[20,22,24].

Other than for a significantly lower relaparotomy rate for intestinal obstruction in patients with J pouches compared with S and W pouches[8], no study has shown a significant difference in surgical complication rates when either J and S[9,23], J and W[10] or S and W[28] pouch designs were compared. Hospital stay was significantly longer in patients with S pouches and may be due to the fact that many S pouches were constructed earlier in the series.

Most patients prefer IPAA to a conventional ileostomy[29,30] and more than 90 per cent of patients were satisfied with the ultimate result of their surgery and preferred it to an ileostomy. Some studies have reported that the 24-h stool frequency of patients with J pouches is significantly higher than that of patients with S[8,9] and W[8] pouches. The results of a small prospective randomized trial comparing the function of J and W pouches showed no difference in bowel frequency or any other aspect of function between the two pouch types[10]. Some series have reported no significant difference in the frequency of defaecation between J and S pouches[20,23].

The W pouch, which takes 1 h longer to construct than a J pouch[10], was developed in the belief that a pouch with a greater capacity would give a lower stool frequency[8]. The present study, in agreement with others[8,31–33], suggests that stool frequency is inversely related to pouch capacity regardless of pouch design. In this series, although the length of bowel used to construct a J pouch was less than that used for S or W pouches, the pouch capacities were similar in the three groups after at least 1 year of follow-up, suggesting that the capacity of J pouches increases after ileostomy closure. Other studies have observed increases in the capacity of J pouches over the 12–18-month period after ileostomy closure[31,34,35]. Such an increase may explain the low stool frequency seen in patients with J pouches in the present study, where function was assessed only in patients with pouches that had been functioning for at least 6 months. Significantly more patients with J pouches were using antidiarrhoeal medication, which may have contributed to their reduced stool frequency. Pouch capacity was not related to the degree of continence but, as in other studies[36,37], there

Table 5 *Maximum tolerated capacity and emptying characteristics*

	J pouch ($n = 6$)	S pouch ($n = 10$)	W pouch ($n = 7$)	*P* J:S	*P* J:W	*P* S:W
Follow-up (months)	58 (14–69)	28 (14–72)	18 (13–38)	<0·05	<0·05	<0·05
No. with pouchitis	2	3	2	n.s.	n.s.	n.s.
Approximate length of bowel used (cm)	30 (30–40)	45 (36–45)	53 (40–54)	<0·001	<0·001	<0·001
Maximum tolerated capacity (ml)	329·5 (203–428)	321·5 (189–450)	317·0 (285–579)	n.s.	n.s.	n.s.
Percentage spontaneous evacuation	28 (7–78)	4 (1–69)	48 (16–70)	<0·01	n.s.	<0·005
Percentage total evacuation	32 (22–83)	51 (2–84)	60 (17–72)	n.s.	n.s.	n.s.

Values are medians with ranges in parentheses; n.s., not significant was a trend towards better continence in patients with preservation of the anal transition zone.

Only 47 per cent of patients with S pouches could empty their pouches spontaneously (similar to the results of Nicholls and Pezim[8] of 41 per cent), and it has become clear that this is as a result of the long efferent segment which can be overcome by constructing a pouch with a short distal segment[9,21,23,38-40]. The patients who needed to catheterize their pouches did not consider it a major disadvantage.

Total percentage evacuation was not significantly different between the three pouch types. Two previous studies have shown that emptying in S and J pouches is similar[32,41], and recently the emptying of W pouches was found to be similar to that for J pouches[42]. The same study[42] also found no relationship between the efficiency of emptying and either stool frequency or degree of continence. O'Connell *et al.*[43] found no association between a poor overall functional result and the completeness of pouch emptying. In the present study, however, more complete pouch evacuation appears to produce a lower nocturnal frequency and better continence. Urgency for defaecation was not related to the efficiency of pouch evacuation. These results are in agreement with other studies which have shown that more complete emptying is associated with better continence[32] and lower stool frequencies[44].

Pouchitis occurred in 21 per cent of patients, all of whom had previously had ulcerative colitis. In agreement with previous reports[12,41,43] this study did not find a relationship between pouchitis and impaired pouch evacuation. It has been suggested that the increased stool frequency in patients with pouchitis is likely to result from decreased pouch capacity and compliance due to inflammation giving rise to oedema and stiffness of the reservoir wall[15]. The present study found no differences in pouch capacity between patients with and without pouchitis. This study has failed to show the increased frequency of pouchitis in patients who had total colitis compared with those who had left-sided disease reported by Farrands *et al.*[45], but patients with ulcerative colitis who had extraintestinal manifestations before IPAA were more likely to develop pouchitis. One other study[46] has reported this finding, although the diagnosis of pouchitis was based only on symptoms without sigmoidoscopic confirmation of pouch inflammation. These findings may be indirect evidence for the hypothesis that immunological mechanisms play a role in the pathogenesis of pouchitis and may have implications for the selection of patients with ulcerative colitis for IPAA.

This study has shown no significant differences in the surgical complication rates, pouch capacity, percentage total evacuation, stool frequency or continence between J, S and W pouch designs. Considering that a high proportion of patients with S pouches could not evacuate their pouches spontaneously and that a greater number of patients with J pouches needed to use antidiarrhoeal medication, W pouches appear to give the best functional result. A good functional outcome after IPAA seems to depend on pouch capacity, the efficiency of pouch emptying and preservation of the anal transition zone.

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References

1. Williams NS, Johnston D. The current status of mucosal proctectomy and ileoanal anastomosis in the surgical treatment of ulcerative colitis and adenomatous polyposis. *Br J Surg* 1985; **75**: 159–68.
2. Williams NS. Restorative proctocolectomy is the first choice elective surgical treatment for ulcerative colitis. *Br J Surg* 1989; **76**: 1109–10.
3. Nicholls RJ, Kamm MA. Proctocolectomy with restorative ileoanal reservoir for severe idiopathic constipation: report of two cases. *Dis Colon Rectum* 1988; **31**: 968–9.
4. Hosie KB, Kmiot WA, Keighley MRB. Constipation: another indication for restorative proctocolectomy. *Br J Surg* 1990; **77**: 801–2.
5. Parks AG, Nicholls RJ. Proctocolectomy without ileostomy for ulcerative colitis. *Br Med J* 1978; **2**: 85–8.
6. Utsunomiya J, Iwama T, Imajo M *et al.* Total colectomy, mucosal proctectomy and ileoanal anastomosis. *Dis Colon Rectum* 1980; **23**: 459–66.
7. Fonkalsrud EW. Endorectal ileal pullthrough with ileal reservoir for ulcerative colitis and polyposis. *Am J Surg* 1982; **144**: 81–7.
8. Nicholls RJ, Pezim ME. Restorative proctocolectomy with ileal reservoir for ulcerative colitis and familial adenomatous polyposis: a comparison of three reservoir designs. *Br J Surg* 1985; **72**: 470–4.
9. Nasmyth DG, Williams NS, Johnston D. Comparison of the function of triplicated and duplicated pelvic ileal reservoirs after mucosal protectomy and ileo-anal anastomosis for ulcerative colitis and adenomatous polyposis. *Br J Surg* 1986; **73**: 361–6.
10. Keighley MRB, Yoshioka K, Kmiot W. Prospective randomized trial to compare the stapled double lumen pouch and the sutured quadruple pouch for restorative proctocolectomy. *Br J Surg* 1988; **75**: 1008–11.
11. Hallgren T, Fasth S, Nordgren S, Oresland T, Hallsberg L, Hulten L. Manovolumetric characteristics and functional results in three different pelvic pouch designs. *Int J Color Dis* 1989; **4**: 156–60.
12. Moskowitz RL, Shepherd NA, Nicholls RJ. An assessment of inflammation in the reservoir after restorative proctocolectomy with ileoanal reservoir. *Int J Color Dis* 1986; **1**: 167–74.
13. Tytgat GNJ, van Deventer SJH. Pouchitis. *Int J Color Dis* 1988; **3**: 226–8.
14. Madden MV, Farthing MJG, Nicholls RJ. Inflammation in ileal reservoirs: 'pouchitis'. *Gut* 1990; **31**: 247–9.
15. Meuwissen SGM, Hoitsma H, Boot H, Seldenrijk CA. Pouchitis (pouch ileitis). *Neth J Med* 1989; **35**: S54–66.
16. Shepherd NA, Jass JR, Duval I, Moskowitz RL, Nicholls RJ, Morson BC. Restorative proctocolectomy with ileal reservoir: pathological and histochemical study of mucosal biopsy specimens. *J Clin Pathol* 1987; **40**: 601–7.
17. O'Connell PR, Kelly KA, Brown ML. Scintigraphic assessment of neorectal motor function. *J Nucl Med* 1986; **27**: 460–4.
18. Dozois RR, Goldberg SM, Rothenberger DA *et al.* Symposium: restorative proctocolectomy with ileal reservoir. *Int J Color Dis* 1986; **1**: 2–19.
19. Pemberton JH, Kelly KA, Beart RW, Dozois RR, Wolff BG, Ilstrup DM. Ileal pouch–anal anastomosis for chronic ulcerative colitis. *Ann Surg* 1987; **206**: 504–13.
20. Fleshman JW, Cohen Z, McLeod RS, Stern H, Blair J. The ileal reservoir and ileoanal anastomosis procedure. *Dis Colon Rectum* 1988; **31**: 10–16.
21. Wexner SD, Jensen L, Rothenberger DA, Wong WD, Goldberg SM. Long-term functional analysis of the ileoanal reservoir. *Dis Colon Rectum* 1989; **32**: 275–81.
22. Taylor BA, Dozois RR. The J ileal pouch–anal anastomosis. *World J Surg* 1987; **11**: 727–34.
23. Pescatori M, Mattana C, Castagneto M. Clinical and functional results after restorative proctocolectomy. *Br J Surg* 1988; **75**: 321–4.
24. Everett WG. Experience of restorative proctocolectomy with ileal reservoir. *Br J Surg* 1989; **76**: 77–81.
25. Wong WD, Goldberg SM. The 'S' pouch. In: Lee ECG, ed. *Surgery of Inflammatory Bowel Disorders*. Edinburgh: Churchill Livingstone, 1987: 81–95.
26. Oresland T, Fasth S, Nordgren S, Hulten L. The clinical and functional outcome after restorative proctocolectomy. *Int J Color Dis* 1989; **4**: 50–6.
27. Pezim ME, Pemberton JH, Beart RW *et al.* Outcome of 'indeterminant' colitis following ileal pouch–anal anastomosis. *Dis Colon Rectum* 1989; **32**: 653–8.
28. Harms BA, Pahl AC, Starling JR. Comparison of clinical and compliance characteristics between S and W ileal reservoirs. *Am J Surg* 1990; **150**: 34–8.
29. Pezim ME, Nicholls RJ. Quality of life after restorative proctocolectomy with pelvic ileal reservoir. *Br J Surg* 1985; **72**: 31–3.
30. Pemberton JH, Phillips SF, Ready RR, Zinmeister AR, Beahrs OH. Quality of life after Brooke ileostomy and ileal pouch–anal anastomosis. *Ann Surg* 1989; **209**: 620–8.
31. Becker JM, Hillard AE, Mann FA, Kestenberg A, Nelson JA. Functional assessment after colectomy, mucosal protectomy, and endorectal ileoanal pull-through. *World J Surg* 1985; **9**: 598–605.

32. Nasmyth DG, Johnston D, Godwin PGR, Dixon MF, Smith A, Williams NS. Factors influencing bowel function after ileal pouch–anal anastomosis. *Br J Surg* 1986; **73**: 469–73.
33. Oresland T, Fasth S, Nordgren S, Akervall S, Hulten L. Pouch size: the important functional determinant after restorative proctocolectomy. *Br J Surg* 1990; **77**: 265–9.
34. Hulten LAG. Symposium: Restorative proctocolectomy with ileal reservoir. *Int J Color Dis* 1986; **1**: 2–19.
35. Dozois RR. Symposium: Restorative proctocolectomy with ileal reservoir. *Int J Color Dis* 1986; **1**: 2–19.
36. Johnston D, Holdsworth PJ, Nasmyth DG *et al.* Preservation of the entire anal canal in conservative proctocolectomy for ulcerative colitis: a pilot study comparing end-to-end ileo-anal anastomosis without mucosal resection with mucosal protectomy and endo-anal anastomosis. *Br J Surg* 1987; **74**: 940–4.
37. Miller R, Bartolo DCC, Orrom WJ, Mortensen NJMcC, Roe AM, Cervero F. Improvement of anal sensation with preservation of the anal transition zone after ileoanal anastomosis for ulcerative colitis. *Dis Colon Rectum* 1990; **33**: 414–18.
38. Pescatori M, Manhire A, Bartram C. Evacuation pouchography in the evaluation of ileoanal reservoir function. *Dis Colon Rectum* 1983; **26**: 365–8.
39. Cohen Z. Symposium: Restorative proctocolectomy with ileal reservoir. *Int J Color Dis* 1986; **1**: 2–19.
40. Nicholls RJ, Gilbert JM. Surgical correction of the efferent ileal limb for disordered defaecation following restorative proctocolectomy with the S ileal reservoir. *Br J Surg* 1990; **77**: 152–4.
41. Heppell J, Belliveau P, Taillefer R, Dube S, Derbekyan V. Quantitative assessment of pelvic ileal reservoir emptying with a semisolid radionuclide enema. *Dis Colon Rectum* 1987; **30**: 81–5.
42. Kmiot WA, Yoshioka K, Pinho M, Keighley MRB. Videoproctographic assessment after restorative proctocolectomy. *Dis Colon Rectum* 1990; **33**: 566–72.
43. O'Connell PR, Rankin DR, Weiland LH, Kelly KA. Enteric bacteriology, absorption, morphology and emptying after ileal pouch–anal anastomosis. *Br J Surg* 1986; **73**: 909–14.
44. Stryker SJ, Phillips SF, Dozois RR, Kelly KA, Beart RW. Anal and neorectal function after ileal pouch–anal anastomosis. *Ann Surg* 1986; **203**: 55–61.
45. Farrands PA, Shepherd NA, Nicholls RJ. Ileal reservoir inflammation (pouchitis) after restorative proctocolectomy ileal reservoir. *Gut* 1988; **29**: A1486 (Abstract).
46. Lohmuller JL, Pemberton JH, Dozois RR, Illstrup D, van Heerden J. Pouchitis and extraintestinal manifestations of inflammatory bowel disease after ileal pouch–anal anastomosis. *Ann Surg* 1990; **211**: 622–7.

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Necrotizing enterocolitis following operation in the neonatal period

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Over a 16-year period, 33 newborn infants developed necrotizing enterocolitis (NEC) following some form of operation (accounting for 19 per cent of all neonates with NEC), including repair of myelomeningocele, intestinal atresia, gastroschisis and congenital diaphragmatic hernia. The neonates with postoperative NEC had a median birth-weight of 3·05 (range 1·0–4·4) kg, and median gestational age of 40 (range 27–41) weeks. Twenty patients were treated non-operatively. The remaining 13 required operation for complications of NEC. Twenty-three patients are alive and have been followed for a median of 66 (range 3–168) months. If a neonate deteriorates following any operation NEC must be included in the differential diagnosis.

Necrotizing enterocolitis (NEC) is a major cause of mortality and morbidity among newborn infants and is one of the most common neonatal conditions requiring an emergency abdominal operation[1,2]. While low birth-weight infants who have been stressed during the perinatal period are particularly susceptible to NEC, the disease may also occur following an operation at any age. In 1968, Tanner and Hardy reported acute necrotizing enterocolitis in adults following gastric surgery[3] and in infants this may occur after cardiac[4,5], abdominal[6,7] and spinal surgery[8].

This paper emphasizes NEC as a possible postoperative complication in the neonate and reviews the clinical presentation, management and pathogenesis in these patients.

Patients and methods

The case notes of all patients who developed NEC after an operation between 1974 and 1989 were reviewed retrospectively. Gestational age, birth-weight, initial diagnosis and operation, clinical and radiological features of NEC, and operative or autopsy findings were recorded. Only patients with diagnostic radiological, operative or autopsy evidence of NEC (Bell stage II or III)[9] were included in the study. Patients who had isolated perforation of the bowel or enterocolitis associated with Hirschsprung's disease were excluded.

Patients with NEC were treated with nasogastric decompression, intravenous fluids and broad spectrum antibiotics. Laparotomy was undertaken when there was evidence of intestinal perforation, or progressive transmural disease suggested by general deterioration, increasing abdominal tenderness, a tender abdominal mass, erythema of the abdominal wall, a persistent dilated loop of bowel on radiographic examination or progressive metabolic acidosis. Usually resection of the involved segment of bowel and formation of proximal and distal enterostomies were carried out. Primary anastomosis was not done. Operation was withheld from neonates who were moribund and considered to have extensive intestinal necrosis unless their condition improved and anaesthetic risks became acceptable.

Results

A total of 175 patients with proven NEC were treated in the Regional Neonatal Surgical Unit at the Royal Liverpool Children's Hospital at Alder Hey during the 16-year period under review. Of these patients, 33 (19 per cent) developed NEC after an operation.

The infants with postoperative NEC had a median birth-weight of 3·05 (range 1·0–4·4) kg and median gestational age of 40 (range 27–41) weeks. Only two infants weighed less than 2 kg at birth. General anaesthesia for neonatal surgery in this hospital is routinely administered by an anaesthetic team led by a consultant paediatric anaesthetist. There were no records of untoward events, e.g. hypoxia or hypotension, occurring during the first operation in any infant who developed postoperative NEC. The NEC developed at a median of 3 (range 1–23) days after operation and a median postnatal age of 5 (range 2–69) days. Most patients (25 out of 33) had delayed onset of oral feeding because their primary condition required operation on the first day of life. Eight patients (five with hydrocephalus, two with inguinal hernia and one with congenital heart disease) had normal onset of oral feeding. In this retrospective review the data relating to whether breast milk had been used in feeding was incomplete. There was no consistent pattern in the organisms cultured from the nasogastric aspirate or stools.

The initial diagnoses and surgical procedures in neonates who subsequently developed NEC are summarized in *Table 1*. The majority had operations for major congenital anomalies. Three had relatively minor procedures, including one who had anal cutback and two who had elective herniotomy for inguinal hernia.

Twenty patients were managed non-operatively during the acute phase of the disease, one of whom subsequently required resection of a small intestinal stricture. Thirteen patients had evidence of complications and had resection of the involved bowel segment. The indications for operation were perforation in 11 patients and transmural necrosis without perforation in two patients.

Of the 33 patients, 23 are alive, including 10 who had an operation for complications of NEC. Follow-up has been for a median of 66 (range 3–168) months. No patients have residual symptoms attributable to the NEC.

Ten patients died, three of whom had undergone an

Table 1 *Initial diagnosis and operative procedures in 33 neonates who subsequently developed necrotizing enterocolitis*

Diagnosis	*n*	Operation
Spina bifida	12	Primary closure
Hydrocephalus	5	Ventriculoperitoneal shunt
Congenital diaphragmatic hernia	5	Primary repair
Intestinal atresia	2	Primary repair
Anorectal anomaly	2	Transverse colostomy (*n* = 1), Anal cutback (*n* = 1)
Gastroschisis	2	Primary repair
Oesophageal atresia	2	Oesophagostomy and gastrostomy (*n* = 1) Gastrostomy (*n* = 1)
Inguinal hernia	2	Inguinal hernia repair
Congenital heart disease	1	Cardiac catheterization

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operation for complications of NEC. Nine deaths occurred at a median of 2 days after diagnosis (range 1–17 days) as a result of septicaemia complicating NEC. The other death was due to pneumonia. At autopsy ($n = 9$), the extent of involvement of the bowel with NEC was not uniform. Four patients had full thickness necrosis of the jejunum or ileum while the remaining five had extensive NEC with involvement of the ileum and/or the whole colon. The histological findings were consistent with the diagnosis of NEC.

Two of the 33 infants had recurrent postoperative NEC. The initial abnormality in one was gastroschisis with intestinal atresia and in the other was multiple atresias of the gastrointestinal tract. Each of the recurrent episodes of NEC presented with rectal bleeding without systemic signs of infection. Radiographs demonstrated pneumatosis of the bowel which was extensive on some occasions. The pneumatosis resolved rapidly on discontinuing oral feeds and commencing nasogastric aspiration, intravenous fluids and antibiotics. Ultimately, both infants were successfully weaned on to oral feeds.

Discussion

Necrotizing enterocolitis is primarily a disease of low birth-weight infants occurring at 7–14 days of age following initiation of oral feeds. It is notable that the median birth-weight in the present series was 3·05 kg and only two infants weighed less than 2 kg at birth. Postoperative NEC presented early after operation (median of 3 days) and at an earlier postnatal age (median of 5 days) than usual. There were only three premature infants (gestational age <37 weeks).

Amoury *et al.*[6] were among the first to report NEC after an abdominal operation in infants. Subsequently Mollitt and Golladay[7] described postoperative NEC in 11 newborn infants which included seven patients with gastroschisis. A previous report from this institution identified 19 patients with postoperative NEC of whom 11 had a myelomeningocele[8]. The predominance of neural tube defects persists, and spina bifida and hydrocephalus account for half our patients with postoperative NEC.

There were two patients with gastroschisis, both of whom presented late (3 weeks) in the postoperative period. A high incidence of NEC following repair of gastroschisis has been reported previously. Oldham *et al.* described 54 infants with gastroschisis, ten of whom developed 21 episodes of NEC[10]. In their series NEC had a benign course and only one of 21 episodes required an operation. Delay in initiating enteral feeding (>30 days) as a result of postoperative ileus may lead to stasis and bacterial overgrowth. The intestinal wall in patients with gastroschisis may be predisposed to NEC because the fibrinous peel investing the gut necessitates a higher perfusion pressure to ensure an adequate microcirculation[6,7].

Neonates with intestinal atresia, particularly those with the apple-peel anomaly, may be prone to ischaemia of the gut because of a precarious blood supply[6]. Lafferty *et al.*[11], reporting 76 infants with small bowel atresia, found that NEC was an important cause of morbidity following operation and occurred proximal or distal to the anastomosis. They suggested that if an infant deteriorates postoperatively, and meningitis and pulmonary problems have been excluded, a second look laparotomy should be performed to exclude anastomotic complications or NEC.

Lloyd[12] and Touloukian *et al.*[13] postulated that NEC was preceded by intestinal ischaemia induced by redistribution of cardiac output during hypoxic episodes. Selective intestinal ischaemia may occur during periods of hypoxia in children with congenital diaphragmatic hernia.

Early oral feeding with formula milk may be a factor in the pathogenesis of NEC[14] and breast feeding may have a protective role[14]. There were no reliable data in the present study to assess this factor.

Unlike primary NEC in term infants, which usually does not involve the small bowel[15], the distribution of postoperative NEC does not differ from that of primary NEC in premature infants. In the present series many patients had involvement of both small and large bowel. The diagnosis is confirmed by radiographs and management is identical: intestinal rest and anti-microbials, with operation for perforation or gangrene.

Postoperative NEC is a serious condition with overall survival rates between 33 per cent[6] and 69 per cent (present study), compared with 60–90 per cent in premature infants with primary NEC[9,16–18], and 80–90 per cent for term or older infants with primary NEC[19,20]. The long-term problems of infants with NEC are primarily those related to prematurity[21]. As there were relatively few premature infants in the present study the general outlook for infants who survive postoperative NEC is likely to be good in the long term.

Any operation on a neonate can predispose to the development of postoperative NEC and this diagnosis should be considered, particularly when there is associated abdominal distension, and passage of blood and mucus *per rectum*.

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References

1. Rowe MI. Necrotising enterocolitis. In: Welch KJ, Randolph JG, Ravitch MM, O'Neill JA, Rowe MI, eds. *Pediatric Surgery*. Chicago: Year Book Medical Publishers Inc., 1986: 944–58.
2. Lister J, Tam PKH. Neonatal necrotising enterocolitis. In: Lister J, Irving I, eds. *Neonatal Surgery*. London: Butterworths, 1990: 485–98.
3. Tanner NC, Hardy KJ. Acute necrotising enterocolitis: survival following perforation and resection in two postoperative patients. *Br J Surg* 1968; **55**: 379–81.
4. Kleinman PK, Winchester P, Brill PW. Necrotising enterocolitis after open heart surgery employing hypothermia and cardiopulmonary bypass. *AJR* 1976; **127**: 757–60.
5. Silane MF, Symchych PS. Necrotising enterocolitis after cardiac surgery: a local ischemic lesion? *Am J Surg* 1977; **133**: 373–6.
6. Amoury RA, Goodwin CD, McGill CW, Smith TH, Ashcraft KW, Holder TM. Necrotising enterocolitis following operation in the neonatal period. *J Pediatr Surg* 1980; **15**: 1–8.
7. Mollitt DL, Golladay ES. Postoperative neonatal necrotising enterocolitis. *J Pediatr Surg* 1982; **17**: 757–63.
8. Irving IM, Pabst FL. Neonatal necrotising enterocolitis following surgery for spina bifida. *Z Kinderchir* 1982; **37**: 165–7.
9. Bell MJ, Ternberg JL, Feigin R *et al.* Neonatal necrotising enterocolitis: therapeutic decisions based on clinical staging. *Ann Surg* 1978; **187**: 1–7.
10. Oldham KT, Coran AG, Drongowski RA, Baker PJ, Wesley JR, Polley TZ Jr. The development of necrotising enterocolitis following repair of gastroschisis: a surprisingly high incidence. *J Pediatr Surg* 1988; **23**: 943–9.
11. Lafferty K, Brereton RJ, Wright VM. Necrotising enterocolitis in small bowel atresia. *Z Kinderchir* 1983; **38**: 224–7.
12. Lloyd JR. The etiology of gastrointestinal perforations in the newborn. *J Pediatr Surg* 1969; **4**: 77–84.
13. Touloukian RJ, Posch JN, Spencer R. The pathogenesis of ischemic gastroenterocolitis of the neonate: selective gut mucosal ischaemia in asphyxiated neonatal piglets. *J Pediatr Surg* 1972; **7**: 194–204.
14. Lucas A, Cole TJ. Breast milk and neonatal necrotising enterocolitis. *Lancet* 1990; **336**: 1519–23.
15. Andrews DA, Sawin RS, Ledbetter DJ, Schaller RT, Hatch EI. Necrotising enterocolitis in term infants. *Am J Surg* 1990; **159**: 507–9.
16. Ross MN, Wayne ER, Janik JS, Hanson JB, Burrington JD, Chang JHT. A standard of comparison for acute surgical necrotising enterocolitis. *J Pediatr Surg* 1989; **24**: 998–1002.

17. O'Neill JA, Holcomb GW. Surgical experience with neonatal necrotising enterocolitis. *Ann Surg* 1979; **189**: 612–19.
18. Freeman RB, Lloyd DJ, Miller SS, Duffty P. Surgical treatment of necrotising enterocolitis: a population based study in the Grampian region, Scotland. *J Pediatr Surg* 1988; **23**: 942–4.
19. West KW, Rescorla FJ, Grosfield JL, Vane DW. Pneumatosis intestinalis in children beyond neonatal period. *J Pediatr Surg* 1989; **24**: 818–22.
20. Leonidas JC, Hall RT. Neonatal pneumatosis coli: a mild form of neonatal necrotising enterocolitis. *J Pediatr* 1976; **89**: 456–9.
21. Jackman S, Brereton RJ, Wright VM. Results of surgical treatment of neonatal necrotising enterocolitis. *Br J Surg* 1990; **77**: 146–8.

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Laser-assisted laparoscopic excision of liver cyst

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Laparoscopy has been practised for many years by enthusiastic centres but until recently has been largely neglected by the surgical community as a whole. With the recent introduction of laparoscopic cholecystectomy[1], the possibility of undertaking other procedures using this technique has now reached a much broader surgical audience[2–4]. We report here the laparoscopic excision of two liver cysts in a patient with symptomatic polycystic liver disease.

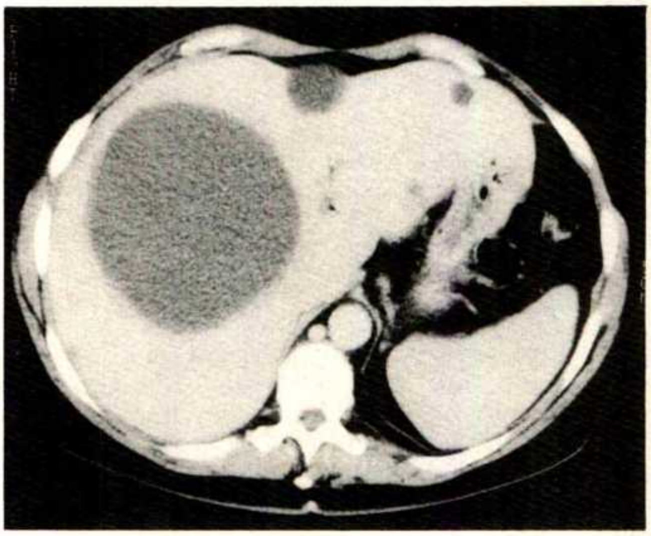

Figure 1 *Computed tomographic scan showing large 16-cm diameter thick-walled cyst in the right lobe of the liver with a thin-walled cyst 4 cm in diameter in the left lobe*

Patients and methods

A 53-year-old woman presented with breathlessness and a raised right hemidiaphragm secondary to acute haemorrhage into a 16-cm diameter cyst, shown on computed tomographic scanning to be within the right lobe of the liver (*Figure 1*). Investigation excluded infectious causes and confirmed the presence of polycystic liver disease. The patient remained symptomatic from the largest of her cysts and was offered excision under laparoscopic guidance.

Under general anaesthesia and endotracheal intubation, laparoscopy was performed with CO_2 insufflation using a 10-mm end-viewing Storz laparoscope (Rimmer Brothers, Clerkenwell, London, UK) introduced through a disposable spring-loaded 10-mm trochar and cannula (Endopath, Ethicon Ltd., Edinburgh, UK) and inserted through a supraumbilical incision. The large cyst in the dome of the right liver was easily identified and surrounding adhesions between it and the diaphragm confirmed the presence of recent inflammation. A second, smaller, thin-walled cyst was seen in the left lobe just to the left of the falciform ligament. Further access to the peritoneum was gained by inserting a second 10-mm port in the epigastrium to the right of the midline and three further 5-mm ports in the right and left subcostal regions.

The cyst wall was incised using a Nd YAG laser scalpel (Sigmacon Ltd., Stanmore, UK). The cyst contents were aspirated and the roof of the cyst was excised by laser dissection. The laser was used through the middle port of the two right subcostal and midline ports, the grasping forceps being manipulated through the adjacent two ports. The excised roof of the cyst was 6 mm deep and was placed within the cystic cavity while the second cyst was excised. Access to this second cyst was achieved by cutting a window through the suprahepatic part of the falciform ligament. Following extraction of the cyst walls, as for laparoscopic cholecystectomy, a small suction drain was inserted through the most lateral right subcostal 5-mm port and placed within the cavity of the larger cyst. The peritoneal cavity was deflated, the instruments were removed and the entry portals closed with a subcuticular suture. The patient made an uneventful recovery and was discharged home on the third postoperative day. Histology confirmed the benign nature of the cyst walls.

Discussion

Surgical intervention for hepatic cysts is seldom indicated but offers the most effective treatment for symptomatic disease. Laparoscopic excision of the cyst roof in the present case considerably reduced the morbidity and hospital stay from that which might have been expected had the procedure been undertaken at open surgery. For thin-walled superficial cysts sharp dissection with scissors or diathermy excision is possible, but when the cyst wall is thick and vascular, laser dissection provides safe, precise and haemostatic dissection.

References

1. Dubois F, Icard P, Berthelot G, Levard H. Coelioscopic cholecystectomy. *Ann Surg* 1990; **211**: 60–2.
2. Leahy PF. Technique of laparoscopic appendicectomy. *Br J Surg* 1989; **76**: 616.
3. Mouret P, Francois Y, Vignal J, Barth X, Lombard-Platet R. Laparoscopic treatment of perforated peptic ulcer. *Br J Surg* 1990; **77**: 1006.
4. Ger R, Monroe K, Duvivier R, Mishrick A. Management of indirect inguinal hernias by laparoscopic closure of the neck of the sac. *Am J Surg* 1990; **159**: 370–3.

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Fibronectin and collagen gene expression in healing experimental colonic anastomoses

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The temporal and spatial expression of fibronectin and type I and III collagen genes were studied 1–14 days after surgery in the healing rat colonic anastomosis using recombinant deoxyribonucleic acid techniques. Messenger ribonucleic acids (mRNAs) coding for fibronectin and type III collagen synthesis increased from the first day after operation and type I collagen synthesis increased from the second day after operation, as demonstrated by Northern hybridizations. Maximal mRNA production for fibronectin and collagens was seen at 2 and 7 days, respectively, after anastomosis. Activation of type I and III collagen genes in the anastomotic area was confined to tissues developing in the anastomotic line, the serosal surface and the submucosal layer. Strong fibronectin expression was observed in the same areas. The results suggest that genetic events leading to collagen synthesis in the anastomotic area start immediately after surgery. Maximal gene expression is not reached until 1 week after surgery.

The submucosa is a tough fibrous structure and is the strongest part of the intestinal wall[1,2]. Early breaking strength of an intestinal anastomosis initially depends on the placement of sutures in this layer and on its reconstitution by the laying down of collagen[3,4]. Immediately after surgery a marked fibronectin reaction has been demonstrated immunohistologically in the repair tissue between the inverted colonic leaves and in the adjacent submucosal layer 0–5 mm from the anastomotic line[5,6]. This reaction is maximal 5 days after surgery[5,6]. During early healing, hydroxyproline concentration decreases in the intestinal anastomotic area despite a simultaneous activation of collagen synthesis[7,8]. The nearby submucosal layer loses much of its original immunohistochemical staining intensity to types I and III collagen[5]. From day 3 these collagens begin to accumulate in the submucosa and in the repair tissue developing in the anastomotic line with the onset of revascularization[6].

Accumulation of fibronectin and types I and III collagen have been documented in the anastomotic area but the heterogeneous structure of the intestinal wall and the long half-life of collagens make it difficult to determine the source and synthesis rates of these extracellular matrix components by immunohistochemistry[5,6]. This study uses recombinant deoxyribonucleic acid (DNA) probes to estimate the time sequence and the rate of synthesis of fibronectin and types I and III collagen by measuring the corresponding messenger ribonucleic acids (mRNAs) in the anastomotic area by Northern hybridization. *In situ* hybridization is used to identify the cellular sources and to estimate the intensity of activation of the genes studied.

Materials and methods

Twenty-two white female Sprague–Dawley rats weighing 216–263 g were used. The animals were allowed to drink and eat *ad libitum* before and after surgery. The colon was not prepared before operation and the animals were not given any premedication. Laparotomy was performed aseptically through a lower abdominal midline incision under intraperitoneal pentobarbital anaesthesia (Mebunat®, Leiras, Finland, 35 mg/kg diluted 1:1 with 0·9 per cent NaCl solution). The sigmoid colon was divided 2·5 cm above the lower peritoneal reflection. Special care was taken not to damage the mesenteric blood vessels. A colocolostomy was performed with 8–10 interrupted 7/0 polypropylene sutures (Prolene®, Ethicon, Germany) using a one-layer inverting submucosal technique. The animals were killed 1, 2, 3, 5, 7 or 14 days after surgery (four per day and two on day 14).

The anastomotic line with 5 mm of colon on either side was removed for study. For control purposes a 10-mm segment of sigmoid colon was removed from four rats without anastomosis. All specimens were gently washed in 0·9 per cent NaCl solution to remove faeces and were then divided longitudinally into equal parts. The specimens for the Northern blots were immediately snap-frozen in liquid nitrogen and those for *in situ* hybridization were fixed in 4 per cent buffered formalin solution at room temperature for 24 h and then dehydrated in rising ethanol series, cleared in xylene and embedded in paraffin.

Hybridization probes

The following complementary DNA (cDNA) clones were used as hybridization probes: clone pα1R2 containing sequences complementary to rat proα1(I) collagen mRNA[9], clone pRGR5 for rat proα1(III) collagen mRNA (J. K. Mäkelä *et al.*, unpublished results), and clone λrlf1 for rat fibronectin mRNA[10]. For *in situ* hybridization the following insert fragments were isolated: a 300 base pair (b.p.) EcoRI-PstI fragment from plasmid pα1R2, a 1600 b.p. EcoRI fragment further digested with TaqI from plasmid pRGR5 and a 400 b.p. EcoRI fragment from plasmid λrlf1. The purified cDNA inserts were labelled with ^{32}P-labelled deoxycytosine 5′-triphosphate for Northern hybridizations and ^{35}S-labelled deoxy(thio)adenosine 5′-triphosphate (ATP) for *in situ* hybridizations using the random priming method[11]. BglI-generated fragments (100–790 b.p.) of bacteriophage λ DNA were labelled and used similarly in the *in situ* hybridization studies; the fragments were used as negative control probes.

RNA extraction and Northern hybridizations

After homogenization total RNA was extracted from each specimen which included the anastomotic line and 5 mm of colon on both sides, or from the control specimens, using the method of Chirgwin *et al.*[12]. Fifteen-microgram aliquots of total RNA (four series consisting of one control specimen and one specimen from each day, 1, 2, 3, 5, 7 and 14 days after anastomosis) were denatured with formamide/formaldehyde and fractionated by electrophoresis on 1 per cent agarose gels containing 2 mol/l formaldehyde, and were then transferred by blotting on to GeneScreen Plus® (DuPont, Wilmington, USA) transfer membranes. The filters were hybridized with ^{32}P-labelled probes. After hybridization the filters were washed and the bound probe was detected by autoradiography at −70°C using intensifying screens. Equal loading was ascertained by densitometric quantification of the ethidium bromide-stained ribosomal RNAs fractionated on the gels (*Figure 1a*). Multiple exposures of the Northern hybridizations were analysed with a densitometer (Ultroscan® XL Enhanced Laser Densitometer, LKB,

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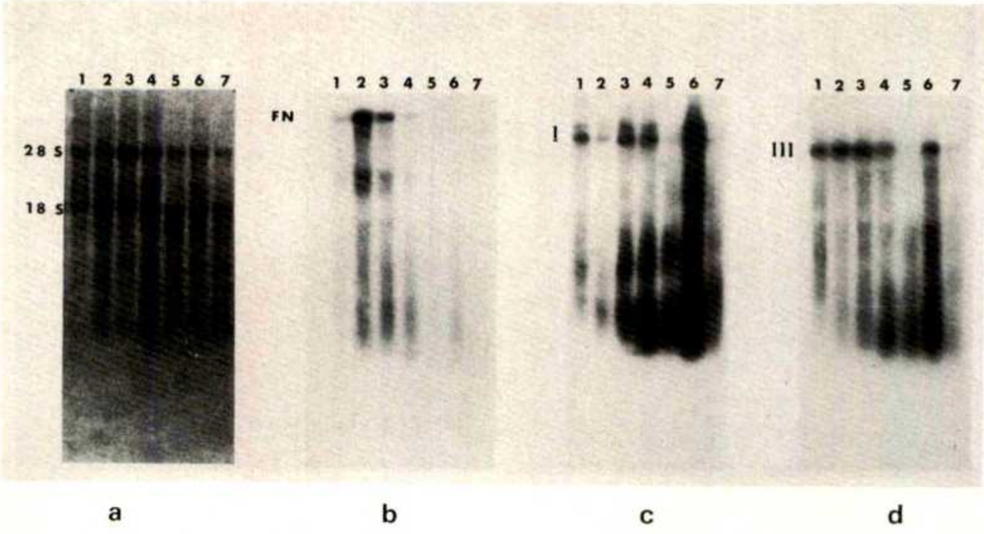

Figure 1 **a** *Ethidium bromide-stained total ribonucleic acids (RNAs) in one series; 18 S and 28 S are the ribosomal fractions.* **b** *Northern hybridizations of fibronectin (FN) messenger RNA (mRNA).* **c** *Proα1(I) collagen mRNA (I).* **d** *Proα1(III) mRNA (III). The RNAs were extracted from the following samples: 1, control; 2, day 1; 3, day 2; 4, day 3; 5, day 5; 6, day 7; 7, day 14 after surgery*

Table 1 *Relative activity of fibronectin and types I and III collagen messenger ribonucleic acid synthesis in the rat colon anastomosis (the anastomotic line and 5 mm of colon on both sides) by mean values of densitometric analysis of the Northern hybridizations. Activity on the first day after operation standardized to 1·00* (n = *4 on each day*)

		Time after anastomosis (days)					
Probe	Control	1	2	3	5	7	14*
Fibronectin	0·45	1·00	1·41	1·32	1·15	0·91	0·07
Collagen type I	1·33	1·00	2·28	6·33	11·71	14·89	3·45
Collagen type II	0·62	1·00	1·38	1·48	2·08	2·31	0·64

* *n* = 2

Sweden) connected to a computer to measure the area produced by each peak (software: GelScan XL (2,1)", Pharmacia LKB Biotechnics AB, Sweden). The results were corrected for minor variations in the amount of ribosomal RNA in the specimens. In each series the activity on the first day after operation was standardized to 1·0. The mean values calculated from four series of specimens are shown in *Table 1*.

In situ *hybridization*

The *in situ* hybridization studies were carried out according to the technique of Sandberg and Vuorio[13]. For *in situ* hybridization 5 μm paraffin sections were cut. The specimens were pretreated with proteinase K, HCl and then acetylated. The hybridizations were performed at 42°C for 20 h using ^{35}S-labelled deoxy(thio)ATP probes, followed by washing, autoradiography for 2–14 days and staining of sections with haematoxylin. To ensure similar hybridization and autoradiography conditions the series (one control specimen and specimens taken 1–7 days after surgery) were placed on the same microscopy slide. Autoradiographic reactions were microscopically estimated in each anastomotic structure (mucosa, muscularis mucosae, submucosa, muscular layers, serosa and the repair tissue in the anastomotic line) by two investigators in a double-blind fashion and were scored as described[5,6] according to the density (= number of autoradiographic grains per field) of autoradiographic grains in the specimens.

Results

General observations

The rats lost 0–10 per cent of their body-weight during the first week after surgery but regained their original weight within the subsequent week. All animals recovered quickly, moved freely and ate well. There were no signs of intestinal obstruction and the animals produced normal faeces from day 2. The abdominal incisions healed without infection, and anastomotic leakage or local abscesses were not seen.

Histology of the healing anastomoses

Healing began on the first day after operation with a strong influx of polymorphonuclear leucocytes, most numerous in the anastomotic line (i.e. the area between the inverted colonic leaves) and in the adjacent submucosa. The inflammatory reaction decreased when moving further away from the anastomotic line. The relative number of polymorphonuclear leucocytes fell from the second day after operation but monocytes, macrophages and fibroblasts increased. Angiogenesis was seen in the repair tissue in the anastomotic line from the third day. From day 5 onwards fibroblast-like cells predominated in the submucosa and in the repair tissue in the anastomotic line.

Mucosal repair was slow and local necrosis was seen in the mucosa near the anastomotic line. A small tissue defect (< 1 mm) was still visible in the mucosa 7 days after surgery. By day 14 the mucosa had healed. Postoperative oedema was mainly confined to the submucosa, normally a relatively narrow structure consisting of loose connective tissue with some fibroblast-like cells. On day 1 the submucosa was highly congested and oedematous. By day 7, this oedema had almost disappeared and numerous new blood vessels were seen in the submucosa and in the repair tissue in the anastomotic line. Two weeks after surgery the submucosal inflammation near the anastomotic line had almost disappeared but the number of fibroblasts and blood vessels remained greater than in normal colon. A strong fibroblast reaction was seen on the serosal surface 0–5 mm from the anastomotic line on days 2–7 after surgery (*Figure 2*).

Northern hybridization of the healing anastomosis

Fibronectin expression. Fibronectin mRNA was synthesized in the early days of healing with maximal production on the second day after surgery when the mean value of the densitometric analysis was 3·2 times higher than in the specimens without surgery. The reaction gradually declined but remained above control level during days 3–7 (*Table 1*, *Figure 1b*). On day 14 fibronectin mRNA synthesis in the anastomotic area was less than in the control specimens.

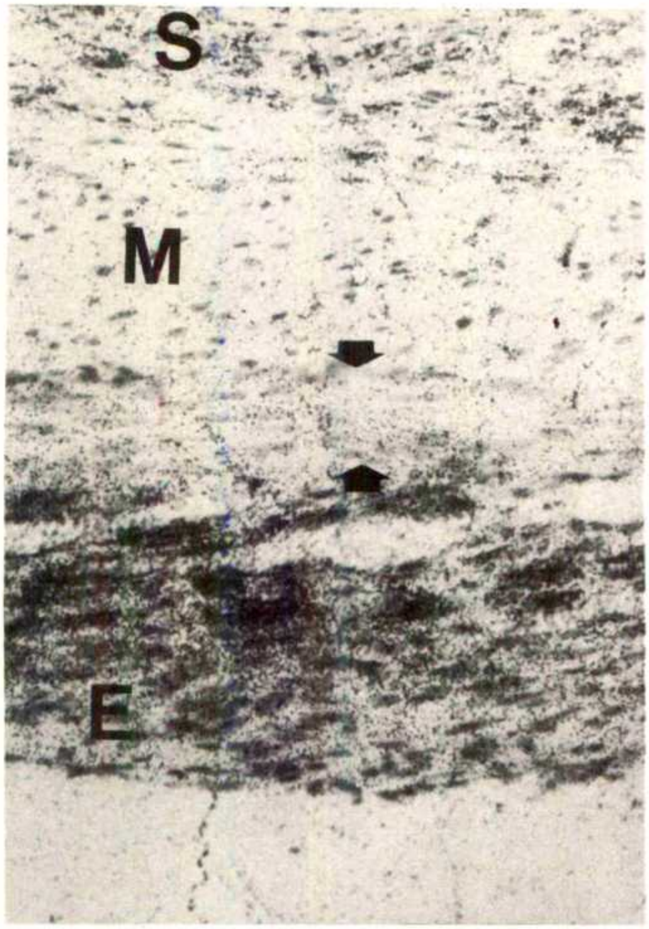

Figure 2 In situ *hybridization of proα1(III) collagen messenger ribonucleic acid on day 7. The intestinal wall is 1–5 mm from the anastomotic line. E, fibroblast reaction on the serosal surface; M, muscle layer; S, submucosa. The arrow indicates the longitudinal muscle layer (original magnification × 110)*

Proα1(I) collagen expression. The reaction to the type I collagen probe increased rapidly from day 2, with the highest level on day 7 (*Table 1, Figure 1c*). The mean densitometric value was almost 15 times higher on day 7 than on day 1 and remained above controls during the 2 weeks.

Proα1(III) collagen expression. The synthesis of type III collagen mRNA increased immediately after anastomosis (*Table 1, Figure 1d*) and was maximal on day 7 when the mean densitometric value was 3·7 times higher than in the control group. Two weeks after surgery the synthesis had returned to the control level.

In situ *hybridizations of the healing anastomosis*

The localizations and intensities of the fibronectin, proα1(I) and proα1(III) collagen gene expressions in the anastomotic area are summarized in *Table 2*.

Fibronectin expression. The submucosa and the repair tissue in the anastomotic line expressed the gene in mononuclear phagocytes and fibroblast-like cells (*Table 2*). Before surgery the circular and longitudinal muscle layers showed a weak reaction similar to that seen in the submucosa. On days 1 and 2 after anastomosis the reaction in the muscle layers became very strong, although in an uneven way, being pronounced in some areas and low in others. The highest activity was confined to areas near the anastomotic line. On day 7 the bound probe in the muscle layer was seen mainly near the mucosal defect in the anastomotic line; elsewhere the reaction was weak.

Proα1(I) and proα1(III) collagen expressions. During the healing process the genes were strongly expressed in fibroblast-like cells in the submucosa (*Figure 3*), the serosal surface (*Figure 2*) and in the granulation tissue in the anastomotic line (*Figure 4*). Elsewhere the reactions were small or absent (*Table 2*).

Discussion

The described technique of colonic anastomosis is easily reproducible without surgical complications[5–8]. Hybridization

Table 2 In situ *hybridizations. Estimation of the amount of autoradiographic grain in the various layers of the anastomotic area (the anastomotic line with 5 mm of colon on both sides)*

		Time after anastomosis (days)				
Area and probe	Control	1	2	3	5	7
Fibronectin						
Mucosa*	(+)	+	+	+	+	(+)
Muscularis mucosae	(+)	+	+	+	(+)	(+)
Submucosa	+	+(+)	++	++	+(+)	+
Muscular layer†	+	+++	+++	+(+)-+++	+(+)-+++	+-++
Serosa	—	—	++(+)	+++	++	+
Anastomosis‡	—	(−)-(+)	++(+)	+++	++	+
Type I collagen						
Mucosa*	((+))	(+)	(+)	(+)	(+)	(+)
Muscularis mucosae	—	—	—	—	—	—
Submucosa	(+)	+	+(+)	++(+)	+(+)	+
Muscular layer†	((+))	((+))	((+))	((+))	((+))	((+))
Serosa	—	+	+	+++	+++	++(+)
Anastomosis‡	—	—	+	++(+)	+++	+++
Type III collagen						
Mucosa*	(+)	++	++	+	+	+
Muscularis mucosae	(+)	(+)	(+)	(+)	(+)	(+)
Submucosa	+	++	++(+)	++	+(+)	+(+)
Muscular layer†	(+)	(+)	(+)	(+)	(+)	(+)
Serosa	—	+	+(+)	++	+++	++
Anastomosis‡	—	(+)	+++	+++	+++	+++

Scale: — (no reaction) to +++ (abundant reaction). * Lamina propria of the mucosa; † circular and longitudinal muscle layers; ‡ repair tissue developing in the anastomotic line between the inverted colonic leaves

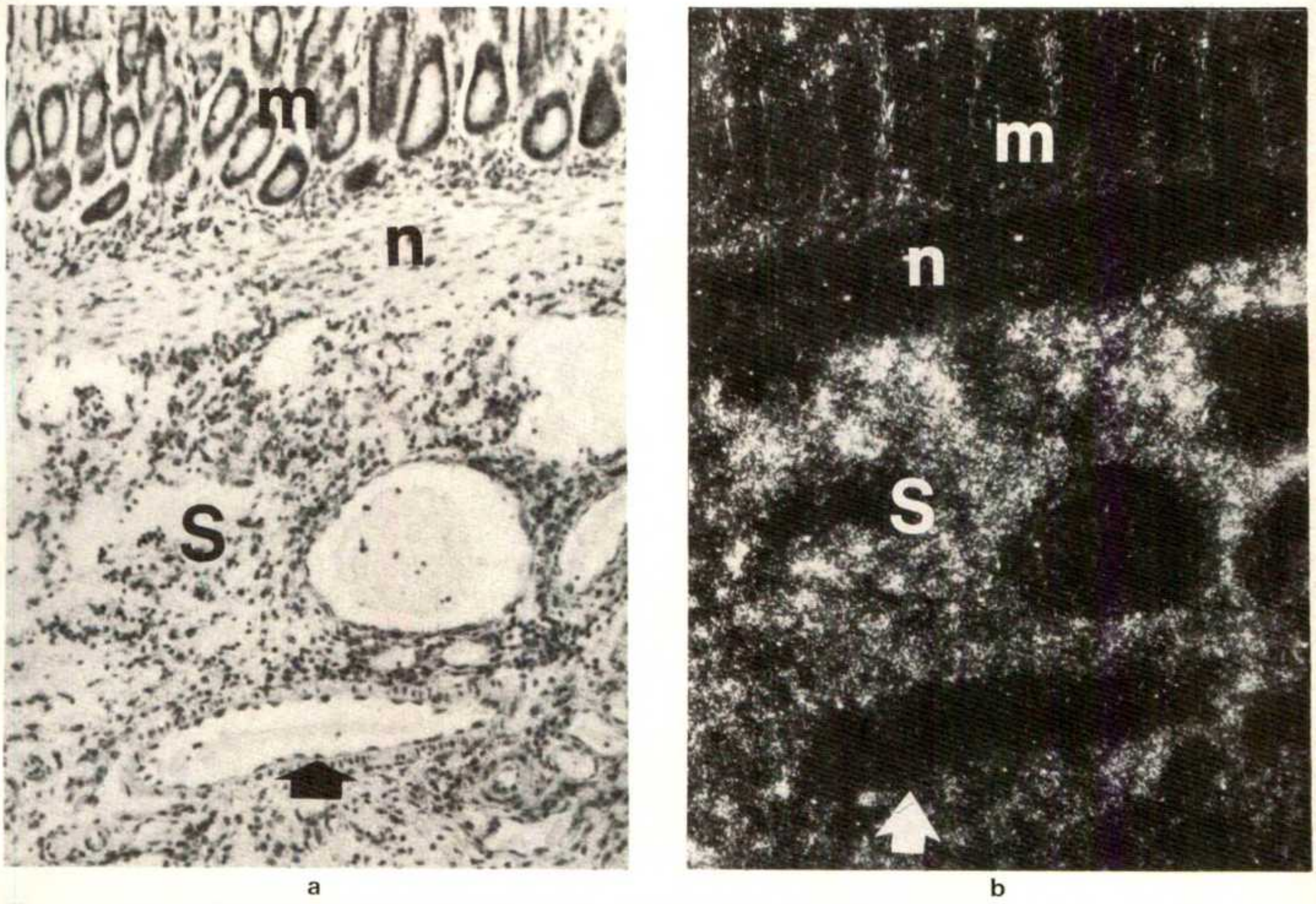

Figure 3 In situ *hybridization of proα1(I) collagen messenger ribonucleic acid on day 3. A part of the submucosal layer 0–5 mm from the anastomotic line is shown.* **a** *Bright field;* **b** *dark field image. m, mucosa; n, muscularis mucosae; S, submucosa. The arrow indicates an engorged blood vessel (original magnification × 200)*

and autoradiography conditions were always the same within one series of specimens and the specificity of the method has been documented[14]. The usefulness of *in situ* hybridization for the localization of metabolically active connective tissue cells is supported by a number of *in vivo* and *in vitro* studies which show that collagen production is mainly regulated at the transcriptional level[15–20]. Modulation at the post-transcriptional level has been described[21].

The Northern hybridizations showed that the first genes to be activated were those for fibronectin and type III collagen, soon followed by that for type I collagen. At least some fibronectin is synthesized locally. These results agree with the observations that mononuclear phagocytes and fibroblasts can produce fibronectin *in vitro*[22–24]. Immunohistological studies have demonstrated that fibronectin is seen in healing colonic anastomoses and in skin wounds immediately after surgery[5,6,25]. Local synthesis of fibronectin is probably not the only source because studies with radioactive fibronectin have shown that plasma fibronectin is sequestrated into damaged tissue[26].

In general, the production of type I and III collagen mRNAs was highest in the same areas as fibronectin mRNA. The collagens were, however, not seen in the smooth muscle layers of the intestinal wall. This contrasts with immunohistological observations in striated abdominal muscle. A great amount of type I and III collagen has been found in the epimysium and perimysium of the muscles of the abdominal wall in silica-induced peritonitis[27].

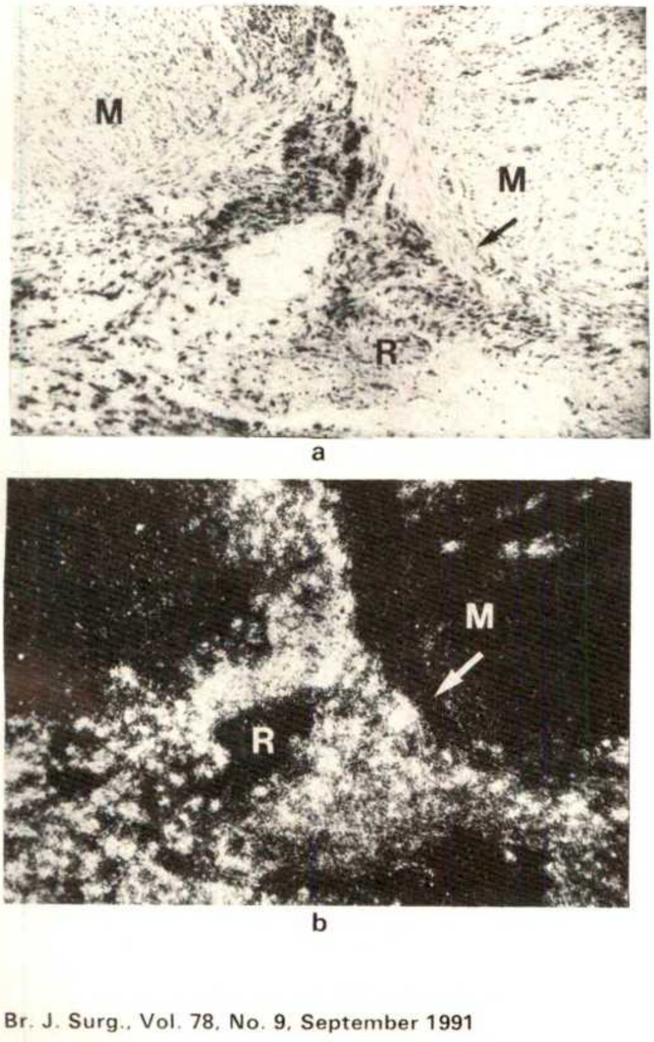

Figure 4 In situ *hybridization of proα1(I) collagen messenger ribonucleic acid on day 3. The anastomotic line near the serosal surface is shown.* **a** *Bright field;* **b** *dark field image. M, muscle layer; R, repair tissue in anastomotic line. The arrow indicates the longitudinal muscle layer (original magnification × 110)*

The expression of type I and III collagen genes is very weak in non-traumatized colon. Our results show that surgical trauma to the intestinal wall activates these genes rapidly. The highest level of gene expression is, however, not seen until 1 week after surgery in the anastomotic area. The transcriptional delay is partly due to the continuous change in the cellular composition of the repair tissue. The increase of type I collagen mRNA was much more pronounced and long lasting than that of type III collagen. Our results suggest that type I collagen synthesis is enhanced for at least 2 weeks after anastomosis whereas type III collagen synthesis is increased only during the first week. These results are in concert with our previous immunohistological studies[5,6] in which the submucosa and the repair tissue in the anastomotic line rapidly accumulated type III collagen from day 2 and type I collagen from day 3 after surgery[5,6]. The mRNA levels of the present study correspond well with the results of our previous immunohistological work[5,6], suggesting that regulation of collagen synthesis in the anastomotic area occurs mainly at the transcriptional level.

In this study type III collagen gene expression preceded that of type I collagen. The same has been observed in early granulation tissue[28–30] when elasticity of the tissue is required. Increase of tensile strength is probably due more to type I than to type III collagen[31]. These collagens are probably synthesized by the same fibroblast-like cells in the injured area, although in different schedules[31]. Recently, copolymers of types I and III collagen have been described in skin, tendon and amnion[32]. It is possible that such copolymers also exist during tissue repair and only the ratio of the two collagen types varies in these mixed fibrils at different stages of repair.

The present results suggest that genetic events, leading to synthesis of extracellular matrix components central to the healing process of the colon anastomoses, start almost immediately after surgery. The synthesis rates of the fibrillar collagens (types I and III) on a cellular and ribosomal level is not maximal until 7 days after anastomosis, which is also the time when reliable anastomotic strength is reached.

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References

1. Halsted WS. Circular suture of the intestine: an experimental study. *Am J Med Sci* 1887; **94**: 436.
2. Lord MG, Valies P, Broughton AC. A morphologic study of the submucosa of the large intestine. *Surg Gynecol Obstet* 1977; **145**: 55–60.
3. Högström H, Haglund U, Zederfeldt B. Suture technique and early breaking strength of intestinal anastomoses and laparotomy wounds. *Acta Chir Scand* 1985; **151**: 441–3.
4. Jönsson K, Jiborn H, Zederfeldt B. Breaking strength of small intestinal anastomoses. *Am J Surg* 1983; **145**: 800–3.
5. Braskén P, Lehto M, Renvall S. Changes in the connective tissue composition of the submucosal layer of colonic anastomosis. *Acta Chir Scand* 1989; **155**: 413–19.
6. Braskén P, Lehto M, Renvall S. Fibronectin, laminin and collagen types I, III, IV and V in the healing rat colon anastomosis. *Ann Chir Gynaecol* 1990; **79**: 65–71.
7. Jiborn H, Ahonen J, Zederfeldt B. Healing of experimental colonic anastomoses. III. Collagen metabolism in the colon after left colon resection. *Am J Surg* 1980; **139**: 398–405.
8. Jiborn H, Ahonen J, Zederfeldt B. Healing of experimental colonic anastomoses. IV. Effect of suture technique on collagen metabolism in the colonic wall. *Am J Surg* 1980; **139**: 406–13.
9. Genovese C, Rowe D, Kream B. Construction of DNA sequences complementary to rat α_1 and α_2 collagen mRNA and their use in studying the regulation of type I collagen synthesis by 1,25-dihydroxyvitamin D. *Biochemistry* 1984; **23**: 6210–16.
10. Schwarzbauer JE, Tamkun JW, Lemischka IR, Hynes OR. Three different fibronectin mRNAs arise by alternative splicing within the coding region. *Cell* 1983; **135**: 421–31.
11. Feinberg AP, Vogelstein B. A technique for radiolabelling DNA restriction endonuclease fragments to high specific activity. *Anal Biochem* 1983; **32**: 6–13.
12. Chirgwin JM, Przybyla AE, McDonald RJ, Rutter WJ. Isolation of biologically active ribonucleic acid from sources enriched in ribonuclease. *Biochemistry* 1979; **18**: 5294–9.
13. Sandberg M, Vuorio E. Localization of types I, II and III collagen mRNAs in developing human skeletal tissues by *in situ* hybridization. *J Cell Biol* 1987; **104**: 1077–84.
14. Kravis D, Upholt WB. Quantitation of type II procollagen mRNA levels during chick limb differentiation. *Dev Biol* 1985; **108**: 164–72.
15. Kosher RA, Kulyk WM, Gay SW. Collagen gene expression during limb cartilage differentiation. *J Cell Biol* 1986; **102**: 1151–6.
16. Raghow R, Gossage D, Seyer JM, Kang AH. Transcriptional regulation of type I collagen genes in cultured fibroblasts by a factor isolated from thioacetamide-induced fibrotic rat liver. *J Biol Chem* 1984; **259**: 12718–23.
17. Rowe DW, Moen RC, Davidson JM, Byers PH, Bornstein P, Palmiter RD. Correlation of procollagen mRNA levels in normal and transformed chick embryo fibroblasts with different rates of procollagen synthesis. *Biochemistry* 1978; **17**: 1581–90.
18. Vuorio T, Mäkelä JK, Vuorio E. Activation of type I collagen genes in cultured sclerodermal fibroblasts. *J Cell Biochem* 1985; **28**: 105–13.
19. Vuorio T, Mäkelä JK, Kähäri V-M, Vuorio E. Coordinated regulation of type I and III collagen production and mRNA levels of proα1(I) and proα2(I) collagen in cultured morphea fibroblasts. *Arch Dermatol Res* 1987; **279**: 154–60.
20. Sandberg M, Mäkelä JK, Multimäki P, Vuorio T, Vuorio E. Construction of a human proα1(III) collagen cDNA clone and localization of type III collagen expression in human fetal tissue. *Matrix* 1989; **9**: 82–91.
21. Focht RJ, Adams SL. Tissue specificity of type I collagen gene expression is determined at both transcriptional and post-transcriptional levels. *Mol Cell Biol* 1984; **4**: 1843–52.
22. Johansson S, Rubin K, Höök M, Ahlgren T, Seljelid R. *In vitro* biosynthesis of coldinsoluble globulin (fibronectin) by mouse peritoneal macrophages. *FEBS Lett* 1979; **105**: 313–16.
23. Tsukamoto Y, Helsel W, Wahl S. Macrophage production of fibronectin, a chemoattractant for fibroblasts. *J Immunol* 1981; **127**: 673–8.
24. Yamada KM, Olden K. Fibronectins – adhesive glycoproteins of cell surface and blood. *Nature* 1978; **275**: 179–84.
25. Viljanto J, Penttinen R, Raekallio J. Fibronectin in early phases of wound healing in children. *Acta Chir Scand* 1981; **147**: 7–13.
26. Gauperaa T, Seljelid R. Plasma fibronectin is sequestrated into tissue damaged by inflammation and trauma. *Acta Chir Scand* 1986; **152**: 85–90.
27. Renvall S, Lehto M, Penttinen R. Development of peritoneal fibrosis occurs under the mesothelial cell layer. *J Surg Res* 1987; **43**: 407–12.
28. Bailey AJ, Shellswell GB, Duance VC. Identification and change of collagen types in differentiating myoblasts and developing chick muscle. *Nature* 1979; **278**: 67–9.
29. Gabbiani G, LeLous M, Bailey AJ, Bazin S, Delaunay A. Collagen and myofibroblasts of granulation tissue. A chemical, ultrastructural and immunologic study. *Virchows Arch [B]* 1976; **21**: 133–45.
30. Lehto M, Duance VD, Restall D. Collagen and fibronectin in a healing skeletal muscle injury. *J Bone Joint Surg [Br]* 1985; **67**: 820–8.
31. Gay S, Martin GR, Muller PK, Timpl R, Kuhn K. Simultaneous synthesis of types I and III collagen by fibroblasts in culture. *Proc Natl Acad Sci USA* 1976; **73**: 4037–40.
32. Keene DR, Sakai LY, Bächinger H-P, Burgeson RE. Type III collagen can be present on banded collagen fibrils regardless of fibril diameter. *J Cell Biol* 1987; **105**: 2393–402.

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Evaluation of palliative surgical procedures in unresectable pancreatic cancer

To update our experience with palliative surgical procedures in unresectable adenocarcinoma of the pancreas, the records of 297 patients surgically treated at Memorial Sloan-Kettering Cancer Center were reviewed. Between October 1983 and November 1989, 117 patients underwent exploratory laparotomy as a single procedure: 24 patients had gastric bypass, 38 biliary bypass, and 118 both gastric and biliary bypass. The postoperative in-hospital mortality rate was 4·4 per cent. Overall morbidity was 20·9 per cent; the morbidity rate in patients with a double bypass was 29·7 per cent. Median(s.e.m.) survival was 231(20·3) days. Statistical analysis showed a significantly increased risk of morbidity in patients who underwent one therapeutic and one prophylactic bypass. Survival was decreased in patients who had a therapeutic gastric bypass (median(s.e.m.) survival 136(70·2) days) or a combination of two therapeutic bypasses (median(s.e.m.) survival 93(85·9) days). These data emphasize the poor prognosis of patients with pancreatic adenocarcinoma who cannot be resected. The need for therapeutic double bypass is a bad prognostic indicator, and a prophylactic bypass added to a therapeutic bypass increases morbidity without prolonging survival.

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Adenocarcinoma of the pancreas has a very poor prognosis. Usually palliative treatment is all that can be offered to patients who present with obstruction of either the extrahepatic biliary tree or the gastric outlet. The majority of patients with adenocarcinoma of the head of the pancreas will develop biliary obstruction in the course of their disease. The most appropriate palliative procedure to relieve the symptoms caused by extrahepatic biliary obstruction appears to be a surgically constructed bypass[1]. In their review of over 8000 patients described in the English literature from 1965 to 1980, Sarr and Cameron conclude that palliation can be provided for up to 5 months, and some patients benefit from their bypass for longer than 1 year[2].

Opinion is divided regarding the preferred procedure. Although a cholecystenterostomy is a simple and expeditious technique, the cystic duct enters the common bile duct near the duodenum in approximately 10 per cent of patients and is thus susceptible to obstruction by local tumour extension. Palliative biliary decompression, using the common hepatic duct, has been advocated[3] and this type of bypass carries the least risk of ascending cholangitis. In some patients survival time after this procedure is as long as that obtained after pancreaticoduodenectomy. However, the median survival after bypass is only 4 months, whereas the median survival after resection is 18 months[4]. The need for a palliative gastric bypass is not always as obvious as the need to perform a biliary bypass. Complete duodenal obstruction is an unusual presenting symptom of pancreatic cancer, but is often a component of the disease. Approximately 30 per cent of patients will present with nausea and vomiting, some of which is associated with duodenal obstruction[5]. There has been considerable debate as to whether gastroenterostomy should be performed in all patients with pancreatic cancer. Some supporters of gastroenterostomy suggest that this should be added when a biliary bypass is performed because it does not increase operative morbidity or mortality rates[6]. A review found that 13 per cent of patients who did not initially have a gastric duodenal bypass subsequently required gastroenterostomy. In contrast, opponents find little need for and no benefit from a gastroenterostomy[7]. Furthermore, it increases the possibility of subsequent stomal ulceration and delayed gastric emptying[8].

We conducted a retrospective study of patients with unresectable pancreatic cancer treated in recent years at Memorial Sloan-Kettering Cancer Center. The impact of various treatment variables on morbidity, postoperative in-hospital mortality rate and survival has been analysed.

Patients and methods

A prospective database was initiated in October 1983 for all patients admitted to the department of surgery with suspected pancreatic and peripancreatic cancer. From October 1983 to October 1989, 983 patients were admitted, 678 of whom had pathologically confirmed adenocarcinoma of the pancreas. Of these, 126 patients were resected and 191 were not explored. Of the remaining 361 patients who were explored but not resected, records with sufficient information to examine the consequences of laparotomy without resection were available for 297. More than 90 per cent of these operations were performed by four surgeons.

Age, sex, preoperative symptoms, operative findings, type of operation performed, postoperative course, presence of delayed gastric emptying after operation, and changes in bilirubin levels after a biliary bypass were recorded. At the time of this review the follow-up status was known in 296 of the 297 patients. The mean overall follow-up of these patients was 165 days (median 99 days, range 5–1138 days). The mean follow-up for survivors was 124 days (median 24 days, range 5–1108 days), and the mean follow-up for patients who died of their disease was 218 days (median 170, range 6–1138 days).

Definitions

Exploratory laparotomy. Laparotomy with the intent for curative resection, with or without a biopsy to establish a diagnosis, but ultimately without resection or the construction of a bypass.

Prophylactic gastric bypass. The procedure performed when there was no clinical or perioperative evidence of obstruction. In the case of a therapeutic gastric bypass, signs of gastric outlet obstruction were present.

Prophylactic biliary bypass. The procedure performed when there was no clinical or biochemical evidence of biliary obstruction (bilirubin

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Table 1 *Presenting symptoms of the 297 patients*

Symptom	No. of patients	Percentage
Weight loss	182	61·3
Pain	163	54·9
Jaundice	155	52·2
Nausea	44	14·8
Vomiting	39	13·1
Anorexia	38	12·8
Diarrhoea	18	6·1
Diabetes	10	3·4
Cholangitis	7	2·4
Other	31	10·4

Table 2 *Treatment or operations preceding treatment at Memorial Sloan-Kettering Cancer Center (MSKCC)*

MSKCC operation	Previous therapy	*n*
Exploratory laparotomy (*n* = 117)	Biliary bypass	18
	Double bypass	14
	Gastric bypass	3
	Exploratory laparotomy	4
	Two-thirds gastrectomy	1
	Cholecystectomy	1
	Biliary drainage (stent)	3
	Total	44 (38%)
Gastric bypass (*n* = 24)	Biliary bypass	3
	Exploratory laparotomy	1
	Cholecystectomy	1
	Biliary drainage (stent)	3
	Total	8 (33%)
Biliary bypass (*n* = 38)	Gastric bypass	3
	Biliary drainage (stent)	3
	Total	6 (16%)
Double bypass (*n* = 118)	Tube cholecystostomy	3
	Cholecystectomy	2
	Biliary bypass	1
	T-tube decompression	1
	Biliary drainage (stent)	11
	Total	18 (15%)

< 1 mg/dl (17 μmol/l). In a therapeutic biliary bypass the bilirubin level was > 1 mg/dl.

Delayed gastric emptying. This occurred when the patient was not able to tolerate oral fluids within 1 week of operation.

Postoperative morbidity. Any event after operation requiring additional medical care; minor events like pulmonary atelectasis and bacteriuria have been excluded.

Postoperative mortality rate. In-hospital mortality rate.

Statistical analysis

The first objective of the statistical analysis was to assess the dependence of morbidity and postoperative mortality rate on explanatory variables. For each endpoint, a univariate analysis was performed by generating independent contingency tables. To test whether morbidity (yes *versus* no) and postoperative in-hospital mortality rate (yes *versus* no) were of equal proportions in the two groups, a χ^2 test or Fisher's exact test was used. Forward stepwise logistic regression and likelihood ratio tests were used to select the variables with the greatest prognostic value as a whole, in a multivariate model, for each endpoint.

The second objective of the statistical analysis was to assess the dependence of the rate of death from unresectable adenocarcinoma of the pancreas on the explanatory variables. Time was measured from date of hospital discharge to the date of death or last follow-up. Survival was estimated for each variable by the product-limit method of Kaplan and Meier[9]. The log rank test was used to check for dependence of survival on each variable taken one at a time[10].

Proportional hazards regression was used to incorporate all the explanatory variables in the same model[11]. Forward stepwise procedures and likelihood ratio tests were used to select the variables with the greatest prognostic value. Cumulative hazard plots were generated to provide a visual check on the assumption of the proportionality of the hazard rates.

The statistical analysis was performed using the BMDP statistical package[12]. The critical significance level of 5 per cent was chosen.

Results

Of the 297 patients analysed, 176 were men and 121 women (ratio 1·45:1) with a median age of 62 years (range 35–86 years). The preoperative symptoms are listed in *Table 1*. Many patients experienced more than one symptom, with weight loss, pain and the development of jaundice as the most frequent combination. This triad was present in 38 patients (12·8 per cent). A weight loss of 5 lb (2·25 kg) or more was noted in 182 patients (61·3 per cent); their median weight loss was 20 lb (9 kg) (range 5–75 lb) (2·25–33·75 kg)). Pain was present in 163 patients (54·9 per cent). Jaundice developed as a symptom in 155 patients (52·2 per cent). Nausea or vomiting was a presenting symptom in 44 (14·8 per cent) and 39 patients (13·1 per cent), respectively. Signs of pancreatic dysfunction were present in 28 patients (9·4 per cent); 18 (6·1 per cent) patients presented with diarrhoea and 10 (3·4 per cent) presented with the adult onset of diabetes mellitus or an increased insulin requirement. The distribution of types of procedure undertaken before referral to our centre is listed in *Table 2*; 76 patients had undergone previous treatment at an outside institution.

In our series, 117 patients (39·4 per cent) underwent an exploratory laparotomy. The other patients had one or two bypasses. Twenty-four patients (8·1 per cent) had gastric bypass as a palliative procedure, 38 patients (12·8 per cent) had biliary bypass, and 118 (39·7 per cent) had both gastric and biliary bypass. Of the total of 156 patients who had a biliary bypass, for 122 (78·2 per cent) it was a therapeutic procedure, and for 34 patients (21·8 per cent) it was a prophylactic procedure. For 28 patients (82 per cent) the prophylactic procedure was performed using the gallbladder, and for six (18 per cent) the common bile duct. The common bile duct was used more often in the case of a therapeutic bypass procedure (75 patients, 61·5 per cent). The gallbladder was used to create a therapeutic bypass in 38 cases (31·1 per cent) and one of the hepatic ducts in seven cases. A choledochoduodenostomy was performed only once. In retrospect, the reasons for the choices of operation could not be determined.

We were not able to show any advantage for one biliary bypass over another with regard to lowering the elevated bilirubin level or relieving the symptoms of jaundice (*Figure 1*). In 16 per cent of the patients with a therapeutic choledochojejunostomy the bypass failed its objective (defined as lowering the bilirubin level to < 2 mg/dl (34 μmol/l) by 10 days after operation). In cases of a therapeutic bypass using the gallbladder, failure occurred in 15·8 per cent. By 10 days only

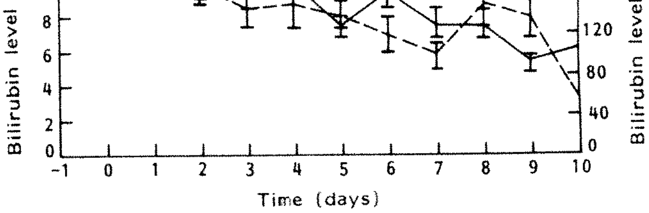

Figure 1 *Bilirubin levels in palliative bypass. Comparison of types of therapeutic biliary bypass. Values are calculated as mean per group, with bars representing the s.e.m. There is no difference in efficacy between choledochojejunostomy (——, n = 70) and cholecystjejunostomy (– – –, n = 35)*

Table 3 *Postoperative complications in treatment groups*

Treatment group	Complication(s)	*n*
Exploratory laparotomy (*n* = 117)	Small bowel ileus	4
	Wound infection	2
	Pancreatic fistula	2
	Cholangitis	1
	Various	6
Gastric bypass (*n* = 24)	Cholangitis	3
	Pneumonia	1
	Respiratory failure	1
	Small bowel ileus	1
Biliary bypass (*n* = 38)	Prolonged jaundice	2
	Bleeding/relaparotomy	1
	Intra-abdominal abscess	1
	Small bowel ileus	1
	Deep vein thrombosis	1
Double bypass (*n* = 118)	Intra-abdominal abscess	9
	Wound infection	4
	Upper gastrointestinal bleeding	4
	Small bowel ileus	3
	Cholangitis	2
	Fever of unknown origin	2
	Pancreatic fistula	1
	Renal failure	1
	Myocardial infarct	1
	Stroke	1
	Intractable pain	1
	Syndrome of inappropriate anti-diuretic hormone secretion	1
	Fluid imbalance	1
	Depression	1
	Urinary retention	3

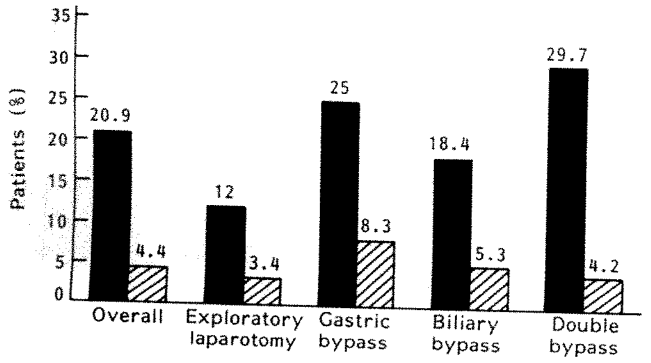

Figure 2 *Morbidity (■) and mortality (▨) rates. Distribution over the treatment groups*

54·3 per cent of patients who underwent a therapeutic biliary bypass had a bilirubin level <2 mg/dl. However, this was dependent on the preoperative level of bilirubin. When the preoperative level of bilirubin was >12 mg/dl (205 μmol/l), 71·4 per cent of patients had levels >2 mg/dl 10 days after bypass. When the preoperative level was <12 mg/dl, 25·9 per cent of patients had bilirubin >2 mg/dl after 10 days.

Table 3 shows morbidity distributed over the treatment groups. The overall percentage of morbidity in this study was 20·9 per cent (*Figure 2*). Postoperative complications were experienced by 29·7 per cent (35 of 118) of patients receiving a double bypass, 25 per cent (six of 24) of the gastric bypass group, 18 per cent (seven of 38) of the biliary bypass group and 12 per cent (14 of 117) of the exploratory laparotomy group.

Delayed gastric emptying (DGE) was seen in 22 patients (7·4 per cent of all patients; *Figure 3*). Most frequently, it occurred after a single gastric bypass (four of 24 patients, 16·7 per cent) and after a double bypass procedure (13 of 118 patients, 11 per cent). The mean duration of DGE was 14 days (median 10 days, range 7–47 days). The duration of DGE distributed over the various groups is shown in *Figure 4*.

Surgical, radiological and endoscopic reinterventions are listed in *Table 4*. While still in hospital, 22 patients (7·4 per cent) underwent a second operation or procedure after the first operation. Two patients who underwent an exploratory laparotomy and one patient who had a biliary bypass as first treatment needed an additional gastric bypass as definitive palliative therapy. Infective complications requiring a second

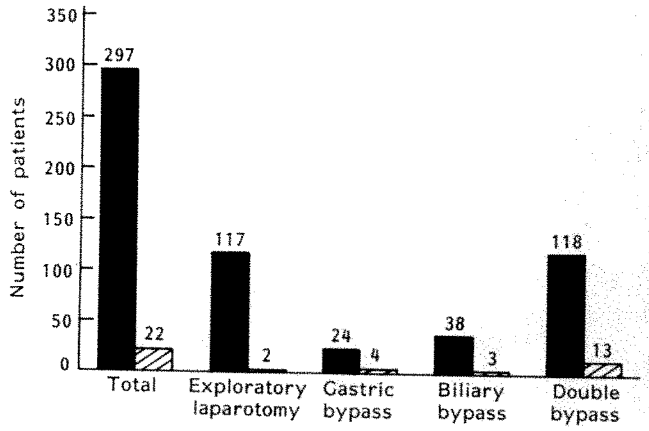

Figure 3 *Delayed gastric emptying. Distribution over the treatment groups:* ■, *total;* ▨, *delayed gastric emptying*

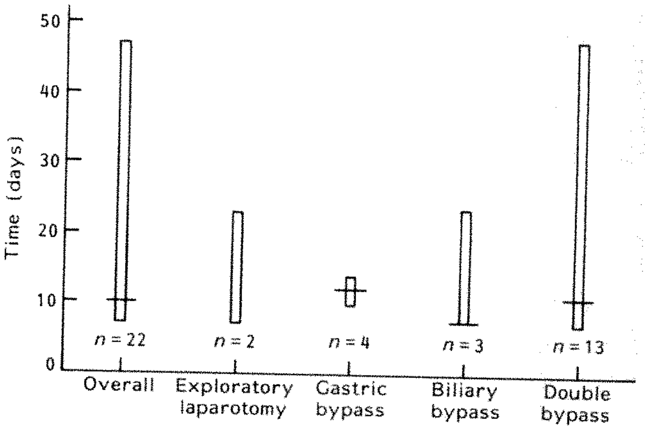

Figure 4 *Comparison of occurrence of delayed gastric emptying over treatment groups. The median and the range of duration of symptoms are indicated*

Table 4 *Surgical, radiological and endoscopic reintervention*

Treatment group	Type of intervention	Total no.
Overall (*n* = 297)		22
After preceding surgery (*n* = 76)		3
Exploratory laparotomy (*n* = 117)	Gastric bypass	2
	Placement of endoprosthesis	1
Gastric bypass (*n* = 24)	Appendicectomy	1
Biliary bypass (*n* = 38)	Gastric bypass	1
	Untwisting volvulus	1
Double bypass (*n* = 118)	Abscess drainage (surgical)	5
	Abscess drainage (percutaneous)	4
	Exploratory laparotomy	2
	Biliary bypass	2
	Gastric bypass	1
	Closure abdominal dehiscence	1
	Ileocolostomy	1

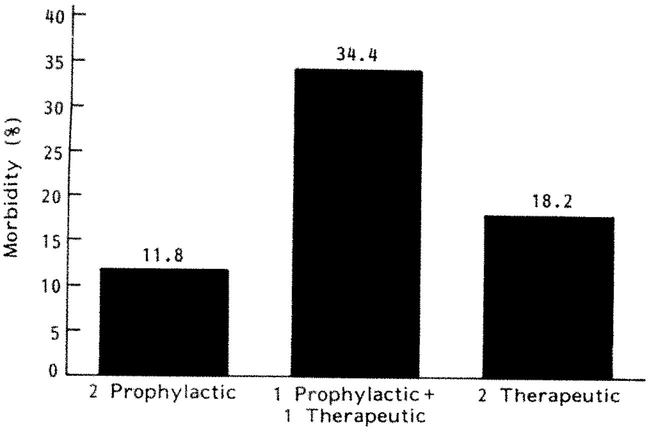

Figure 5 *Comparison of morbidity in patients who underwent a double bypass procedure. Patients with one therapeutic and one prophylactic bypass had a significantly increased risk of morbidity* ($P = 0{\cdot}0022$; χ^2)

Table 5 *Association of relevant variables with regard to morbidity by contingency table analysis*

	Significant correlation at 5% level with	No significant correlation with
Second surgery*	Morbidity	Delayed gastric emptying
	Prolonged hospital stay	Mortality
Prolonged hospital stay	Delayed gastric emptying Morbidity Mortality	
Mortality	Morbidity	Delayed gastric emptying
Morbidity	Delayed gastric emptying	

* At Memorial Sloan-Kettering Cancer Center

operation were found only in the group of patients who underwent a double bypass procedure. In this group five patients (4·2 per cent) had to undergo surgical re-exploration to drain an intra-abdominal abscess; in four others abscesses could be drained using percutaneous techniques.

Overall mean postoperative in-hospital stay was 14 days (median 11, range 4–64). The mean postoperative stay was the shortest for the exploratory laparotomy group (10·2 days, median 9 days, range 4–64 days), and longest for the gastric bypass group (18·1 days, median 15 days, range 7–56 days). Patients who underwent a biliary bypass as a single procedure stayed in hospital for a mean of 14·1 days (median 11 days, range 5–40 days), and those who underwent a double bypass procedure stayed for a mean of 16·9 days (median 13 days, range 6–64 days).

The postoperative in-hospital mortality rate was 4·4 per cent (13 of 297 patients) for the whole series, ranging from 8·3 per cent for the gastric bypass group fo 3·4 per cent for the exploratory laparotomy group (*Figure 2*). The mean survival of these patients was 27·5 days (median 25 days, range 6–64 days).

In analysis of the relation of the investigated variables with morbidity, we found no significant association with age, sex, preoperative weight loss or previous surgery. Of the other variables, DGE was highly associated ($P < 0{\cdot}00001$). When a single bypass procedure was performed, morbidity was not associated with the prophylactic or therapeutic character of the bypass. However, when two bypasses were made, the incidence of morbidity was high (29·7 per cent). In this specific group we have tried to identify a predicting factor for morbidity. As shown in *Figure 5*, it appeared that when two bypasses were made morbidity was significantly higher when one bypass was therapeutic and one was prophylactic, compared with two prophylactic or two therapeutic bypasses ($P = 0{\cdot}0022$). Not surprisingly, both prolonged postoperative hospital stay and morbidity were significantly associated with mortality ($P = 0{\cdot}0018$ and $P < 0{\cdot}00001$ respectively). As some of the investigated variables are interrelated, we performed contingency table analysis to examine the association of relevant variables with morbidity (*Table 5*). In this analysis we found no association between surgical reintervention and DGE or postoperative mortality ($P = 0{\cdot}1040$ and $P = 0{\cdot}8898$ respectively). Prolonged hospital stay was highly associated with DGE ($P < 0{\cdot}00001$), morbidity ($P < 0{\cdot}00001$) and postoperative mortality rate ($P = 0{\cdot}0018$). Mortality was not associated with DGE ($P = 0{\cdot}9680$), but highly correlated with morbidity ($P < 0{\cdot}00001$).

The survival data are listed in *Table 6*. The median(s.e.m.) overall survival was 231(20·3) days. A therapeutic gastric bypass as single procedure and the combination of a therapeutic gastric and a therapeutic biliary bypass had the worst prognosis. The median(s.e.m.) survival for patients who had a therapeutic gastric bypass was 136(70·2) days ($P = 0{\cdot}0418$), but dropped to 93(85·9) days for patients who needed two therapeutic bypasses ($P = 0{\cdot}0096$). The other variables had no impact on survival.

Discussion

Pancreatic cancer continues to increase in incidence, with 27 000 new cases in the USA a year[13]. The surgical treatment of patients with adenocarcinoma of the pancreas remains a controversial subject. Most surgeons favour resection for cure whenever feasible. Although the chances for cure are slim, this operation is thought to provide the best possible palliation and can be performed with acceptable operative mortality rates in specialized centres[5,14]. In some institutions, however, the operative mortality rate is reported to be approximately 20 per cent[13] and overall morbidity 36 per cent[15]. Although resection has been advocated as a palliative procedure, the poor survival data for patients with incomplete resections indicate that a palliative bypass procedure is preferable in such cases[16]. Once a definite diagnosis is established, the problem facing the surgeon is how to provide safe and effective palliation.

It is disappointing that postoperative morbidity and mortality rate after palliative operations, reportedly ranging from 12 to 56 per cent, is similar to that after resection[5]. In our series, the overall morbidity was 20·9 per cent, with an overall in-hospital mortality rate of 4·4 per cent. These figures are more or less favourable, but high for palliative procedures. This is also

Table 6 *Survival*

	No. of patients (%)	Median(s.e.) (days)	P*	P†
Overall	283/283 (100)	231(20·3)		
Exploratory lap	113/283 (39·9)	193(26·3)	0·88	0·38
Gastric bypass	135/283 (47·7)	198(30·5)	0·82	0·69
Therapeutic	27/135 (20)	136(70·2)	0·04‡	0·01‡
Prophylactic	108/135 (80)	249(23·7)		
Biliary bypass	149/283 (52·7)	244(26·1)	0·98	0·34
Prophylactic	31/149 (20·8)	198(40)	0·11	0·61
Therapeutic	118/149 (79·2)	245(29·7)		
Double bypass	112/283 (39·6)	232(27·2)	0·92	0·63
Both prophylactic	16/283 (5·7)	192(57·2)	0·32	0·93
One therapeutic	86/283 (30·4)	258(29·2)	0·16	0·13
Both therapeutic	11/283 (3·9)	93(85·9)	0·01‡	0·01‡
Cholecystjejunostomy	62/140 (44·3)	221(33·5)	0·06	0·24
Choledochojejunostomy	78/140 (55·7)	289(29·2)		

*According to Mantel–Cox statistics; †according to Wilcoxon (Breslow) statistics; ‡significant at the 5 per cent level true in regard to the postoperative hospital stay. The mean overall hospital stay was 14 days, with a longer stay after gastric bypass (18·1 days) and double bypass (16·9 days), clearly reflecting the higher morbidity in these groups (*Figure 2*).

The biliary–enteric bypass should relieve the sequelae of extrahepatic biliary obstruction, but failure rates are high and range from 17 to 28 per cent[1,7]. In our series the proportion of failure was 16 per cent. Current surgical opinion is divided regarding the preferred procedure. After performing a prospective randomized trial, Sarfeh *et al.*[18] concluded that choledochoenterostomy is the superior operation for malignant distal biliary obstruction. Morbidity after choledochoenterostomy was 18·8 per cent compared with a morbidity rate after cholecystoenterostomy of 53 per cent with a 47 per cent incidence of bypass failure. Our data show a morbidity rate of 21 per cent after cholecystjejunostomy and 31 per cent after choledochojejunostomy. In two cases, choledochojejunostomy had to be performed because of persistent jaundice after cholecystjejunostomy. We were unable to demonstrate a difference in efficacy between choledochoenterostomy and a cholecystoenterostomy.

A subject previously not mentioned in detail in other reports is the slow decrease of bilirubin levels after a therapeutic bypass. In our series 54·3 per cent of patients had bilirubin levels >2 mg/dl (34 mol/l) 10 days after bypass and this postoperative decrease was affected by the preoperative bilirubin level. It is as yet unclear whether the duration of antecedent elevated bilirubin levels influences the rate of decline. The significance of this in relation to postoperative morbidity and mortality rate needs further study.

Two recently published small randomized trials favour endoscopically placed endoprostheses as the method of choice for the palliation of malignant obstruction of the distal common bile duct[19,20]. Both trials show a comparable overall survival between endoscopically and surgically bypassed patients. Median survival of patients in both trials, however, was remarkably shorter than the median overall survival of our patients (152 and 84 days, compared with 231 days in our series). The reasons for this difference are not clear, but may be due to patient selection. Episodes of cholangitis (2 per cent in our series) were relatively common in patients with an endoprosthesis (28–43 per cent). Despite this, it seems clear that there is an increasing role for placement of an endoprosthesis, especially in the elderly patient at high surgical risk or the patient who has a limited life expectancy[21].

The use of a gastric bypass has been liberally recommended when patients come to laparotomy[1,5], although at initial presentation only approximately 5 per cent of patients have signs of duodenal obstruction. If a gastric bypass is not performed at initial laparotomy, 10–15 per cent of patients are expected to develop a subsequent duodenal obstruction[2]. Addition of a gastrointestinal bypass is thought not to increase operative morbidity and mortality rates and may prevent the need for reoperation[22]. In our series, 118 patients underwent a double bypass procedure, 90 of whom had one therapeutic bypass and one prophylactic bypass. In 85 the prophylactic bypass was a gastric bypass. In these patients morbidity was significantly increased ($P = 0{\cdot}0022$), which clearly contradicts most previous reports, but agrees with Schantz *et al.*, who observed the same phenomenon[23]. If no gastric bypass was performed, only three patients who returned at a later stage of their disease required it subsequently. Survival of these patients was short, however, with a low probability of a second therapeutic bypass.

Although infrequently discussed in reports of palliative surgical procedures, the occurrence of DGE also appears to be a serious problem after a gastrointestinal bypass. Schantz *et al.* found a 14 per cent incidence of DGE after a combined procedure[23], while Doberneck and Berndt reported a 26 per cent incidence of DGE for periods extending from 9 to 31 days[24]. In our series, DGE occurred in 7·4 per cent of patients, with the majority of cases after a single gastric bypass. Not only is the presence of DGE a significant problem with regard to prolonged hospital stay and patient discomfort, but it was also associated with other morbidity. The precise aetiology of DGE is not known[8]. In none of our patients was vagotomy, frequently thought to be one of the causes, added to the gastrojejunostomy.

Gastric outlet obstruction in pancreatic cancer appears to be a terminal event. In one retrospective study, 90 per cent of patients who had nausea and vomiting with or without impingement on the duodenum as major symptoms had a poor outcome after gastrojejunostomy[7]. The same was seen in our patients. After a therapeutic gastric bypass patient survival was 136 days, significantly shorter than the overall survival time (*Table 6*). Further evidence for the dismal prognosis of patients with gastric outlet obstruction was found in the very short survival time of 93 days for patients in whom two therapeutic bypasses were performed.

A significant percentage of our patients had undergone a previous operative (18·9 per cent) or invasive radiological (6·7 per cent) procedure. In the 117 patients who had an exploratory laparotomy only, 30 per cent had had prior relief of their biliary obstruction (*Table 2*), but 70 per cent had not had an antecedent biliary decompression or gastric bypass. Clearly, these patients were not helped at all by our operation, but fortunately morbidity was low (12 per cent). We were not able to determine the reasons for non-resectability in this group, but a significant number of patients had metastatic disease and may have been ideal candidates for preoperative studies such as laparoscopy.

In summary, our recent experience with palliative surgical procedures in pancreatic carcinoma is disappointing. Prognosis remains dismal, with a 12-month survival of 14·1 per cent (42 patients) and a 24-month survival of only 1·7 per cent (five patients). Two patients (0·7 per cent) survived for 3 years. Postoperative morbidity and mortality rates are unacceptably high for palliative procedures, and the addition of a prophylactic second bypass at the time of the initial palliative surgery further increases these unacceptably high morbidity rates.

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References

1. Sarr MG, Cameron JL. Surgical palliation of unresectable carcinoma of the pancreas. *World J Surg* 1984; **8**: 906–18.
2. Sarr MG, Cameron JL. Surgical management of unresectable carcinoma of the pancreas. *Surgery* 1982; **91**: 123–33.
3. Morgenstern L, Shore JM. Selection of an optimal procedure for decompression of the obstructed common bile duct. *Am J Surg* 1970; **119**: 38–44.
4. Morrow M, Hilaris B, Brennan MF. Comparison of surgical resection, radioactive implantation, and bypass procedure for exocrine carcinoma of the pancreas 1975–1980. *Ann Surg* 1984; **199**: 1–5.
5. Brennan MF, Kinsella T, Friedman M. Cancer of the pancreas. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer, Principles and Practice of Oncology*. 3rd ed. Philadelphia: J. B. Lippincott, 1989: Chapter 26, 800–35.
6. Sarr MG, Gladen HE, Beart RW, van Heerden JA. Role of gastroenterostomy in patients with unresectable carcinoma of the pancreas. *Surg Gynecol Obstet* 1981; **152**: 597–600.

7. Weaver DW, Wiencek RG, Bouwman DL, Walt AJ. Gastrojejunostomy: is it helpful for patients with pancreatic cancer? *Surgery* 1987; **102**: 608–13.
8. Fromm D, Resitarits D, Kozol R. An analysis of when patients eat after gastrojejunostomy. *Ann Surg* 1988; **207**: 14–20.
9. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *Journal of the American Statistics Association* 1958; **53**: 457–81.
10. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemotherapy Reports* 1966; **50**: 163–70.
11. Cox DR. Regression models and life tables (with discussion). *Journal of the Royal Statistical Society* 1972; **34**: 187–220.
12. Dixon WJ. *BMPD Statistical Software*. Berkeley, California: University of California Press, 1985.
13. Beazley RM, Cohn I. Update on pancreatic cancer. *CA* 1988; **38**: 310–19.
14. Trede M, Schwall G, Saeger HD. Survival after pancreaticoduodenectomy: 118 consecutive cases without an operative mortality. *Ann Surg* 1990; **211**: 447–58.
15. Doerr RJ, Yildiz I, Flint LM. Pancreaticoduodenectomy: university experience and resident education. *Arch Surg* 1990; **125**: 463–5.
16. Richards AB, Sosin H. Cancer of the pancreas: the value of radical and palliative surgery. *Ann Surg* 1973; **177**: 325–31.
17. Thompson JF, Walker CJ. The management of pancreatic carcinoma: a review of 173 cases. *Aust NZ J Surg* 1983; **53**: 25–30.
18. Sarfeh IJ, Rypins EB, Jakowatz JG, Juler GL. A prospective, randomized clinical investigation of cholecystoenterostomy and choledochoenterostomy. *Am J Surg* 1988; **155**: 411–14.
19. Shepherd HA, Royle G, Ross APR, Diba A, Arthur M, Colin-Jones D. Endoscopic biliary endoprosthesis in the palliation of malignant obstruction of the distal common bile duct: a randomized trial. *Br J Surg* 1988; **75**: 1166–8.
20. Andersen JR, Sorensen SM, Kruse A, Rokkjaer M, Matzen P. Randomized trial of endoscopic endoprosthesis *versus* operative bypass in malignant obstructive jaundice. *Gut* 1989; **30**: 1132–5.
21. Proctor HJ, Mauro M. Biliary diversion for pancreatic carcinoma: matching the methods and the patient. *Am J Surg* 1990; **159**: 67–71.
22. Potts JR, Broughan TA, Hermann RE. Palliative operations for pancreatiic carcinoma. *Am J Surg* 1990; **159**: 72–8.
23. Schantz SP, Schickler W, Evans TK, Coffey RJ. Palliative gastroenterostomy for pancreatic cancer. *Am J Surg* 1984; **147**: 793–6.
24. Doberneck RC, Berndt GA. Delayed gastric emptying after palliative gastrojejunostomy for carcinoma of the pancreas. *Arch Surg* 1987; **122**: 827–9.

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Bleeding pseudocysts and pseudoaneurysms in chronic pancreatitis

Spontaneous haemorrhage associated with chronic pancreatitis in 17 patients was related to a pseudocyst in 15 (88 per cent) patients and to pancreatic lithiasis (one patient) or to infarction-rupture of the spleen (one patient). Bleeding was massive in six patients and intermittent in 11. It resulted from erosion of the gastroduodenal or the splenic artery in four patients. Bleeding into the pancreatic duct occurred in four patients and erosion of the duodenum by a bleeding pseudocyst in five. Haemorrhage was confined to a pseudocyst in six patients and was intraperitoneal in two. Of the 15 patients with bleeding pseudocysts, ten underwent primary pancreatic resection (eight proximal and two distal pancreatectomies) with no mortality but four had early complications. Four of the five patients who underwent transcystic ligation of bleeding vessels and pseudocyst drainage had postoperative complications: one died from sepsis and liver failure and three underwent reoperation for severe postoperative bleeding. Of these, two had proximal pancreatic resection with one death. The third patient had further suture ligation and external drainage. The overall postoperative mortality rate was 12 per cent and following emergency surgery 33 per cent. Favourable results were achieved in two-thirds of patients when the primary operative strategy could be directed towards the control of bleeding and removal of the affected pancreatic segment. Primary pancreatic resection, although technically demanding in the presence of haemorrhage, is recommended whenever possible for the treatment of bleeding pancreatic pseudocysts and pseudoaneurysms associated with chronic pancreatitis.

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Haemorrhage is an infrequent but well recognized complication in patients with chronic pancreatitis. Pancreatic and peripancreatic inflammation and established pseudocysts can lead to vascular lesions which may cause significant haemorrhage in 2–10 per cent of patients[1–4]. Arterial bleeding into the cyst is reported in 10 per cent of pseudocysts associated with chronic pancreatitis[5]. Erosion of a pseudocyst into vessels incorporated in its wall or into adjacent visceral arteries can result in pseudoaneurysm formation and severe intracystic bleeding with possible rupture into the duodenum, peritoneal cavity, retroperitoneum or pancreatic duct. Complete occlusion of the splenic vein which can lead to segmental portal hypertension and gastrointestinal varices is not uncommon in patients with chronic pancreatitis of long duration[6]. Infarction-rupture of the spleen secondary to splenic vein thrombosis or pseudocyst involvement is a rare but potentially fatal complication[7,8]. Because of its relative rarity, descriptions of spontaneous haemorrhage in patients with chronic pancreatitis have been confined mainly to small series or isolated case reports. Collective experience in patients with this condition observed over the years in various institutions has shown that massive haemorrhage is attended by a high mortality rate even with prompt therapy, and conservative management may be associated with an almost 100 per cent mortality rate[9]. In this study we report our experience in the management of haemorrhage associated with chronic pancreatitis in 17 patients over a period of 17 years.

Patients and methods

Between 1970 and 1986, 23 (14 per cent) of 168 patients treated surgically for chronic pancreatitis in our unit presented with spontaneous bleeding into the upper gastrointestinal tract or peritoneal cavity. Haemorrhage was indirectly related to a pancreatic lesion in six patients (associated peptic ulceration in four patients, portal hypertension and Mallory–Weiss syndrome in one patient each) and these individuals are not considered in this report. In the 17 patients (10 per cent) considered here, haemorrhage arose secondary to severe chronic pancreatitis and occurred into a pseudocyst, the duodenum, common bile duct, pancreatic duct or the free peritoneal cavity. The 13 men and four women ranged in age from 24 to 51 years (mean 43 years). Chronic alcoholism was the main cause in 13 patients, but in four non-alcoholic patients the aetiology was unclear. Duration of symptoms ranged from 2 months to 20 years (mean 5·5 years). None of the reported patients had had previous pancreatic surgery, but cholecystectomy for gallstones and diagnostic laparotomy for unexplained anaemia were carried out in two patients each. Plain abdominal radiology and barium contrast studies were undertaken in all patients at some stage of their disease. Endoscopic retrograde cholangiopancreatography (ERCP), abdominal ultrasonography and/or computed tomography (CT) scans were performed in 11 patients. Preoperative coeliac axis angiography studies were undertaken in eight patients. Intraoperative needle aspiration of pseudocysts to determine the nature of the fluid content and on-table pseudocystography were routinely performed. Proximal pancreatic resection was attempted for bleeding lesions located in the head of the gland and for pseudocysts that had ruptured into the duodenum or pancreatic duct. Distal pancreatectomy was undertaken for bleeding lesions confined to the left pancreas. Non-resectional methods were resorted to mainly in critically ill patients judged unlikely to withstand partial pancreatectomy.

All patients were operated on in one surgical unit by the senior authors (R.P., C.H., M.M.) and all but two of the survivors attended for follow-up at least once a year for 3–12 years (median 6 years).

Data were collected and evaluated in relation to mode of presentation, characteristic of the bleeding lesions, arteriography findings and to the operative findings, procedures and outcome.

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Results

Presentation

Massive haemorrhage into the gastrointestinal tract or peritoneal cavity required urgent operative intervention in six patients (*Table 1*). Early operation was performed in the remaining 11 patients because of intermittent bleeding or anaemia (*Table 2*). Five patients had a palpable abdominal mass which was expanding and pulsatile in two patients. Four patients exhibited marked pancreatic calcification and four patients had associated liver cirrhosis. Three patients had clinical steatorrhoea and two were receiving insulin therapy. Four patients were jaundiced and two had partial duodenal stenosis.

Arteriography findings

Preoperative coeliac axis angiography was undertaken in eight patients mainly to identify a suspected bleeding visceral lesion. Pseudoaneurysm formation secondary to pseudocyst erosion of the gastroduodenal artery (*Figure 1*) was demonstrated in two patients and of the splenic artery in a third patient. Gross displacement and compression of the gastroduodenal artery or the superior mesenteric artery was noted in another two patients. Venous phase films demonstrated portal vein, superior mesenteric vein and splenic vein compression in one patient each. Portal hypertension was documented in one patient.

Operative findings

A total of 20 pancreatic pseudocysts were identified in 15 of the 17 patients, 16 of which were located in the pancreatic head. Bleeding into a pseudocyst was the commonest form of haemorrhage and had occurred in all patients with pseudocysts. The preoperative angiographic findings of pseudocyst-pseudoaneurysm formation were confirmed in three patients. In one patient, who had Wirsung duct bleeding, peroperative pseudocystography showed a large pseudoaneurysm of the gastroduodenal artery within a large pseudocyst in the head of the pancreas with retrograde opacification of the Wirsung duct and possibly the superior mesenteric artery.

Rupture of the bleeding pseudocyst into the duodenum occurred in five patients in one of whom the common bile duct was also eroded.

Bleeding into the Wirsung duct was observed in four patients. In three cases it resulted from erosion of the Wirsung duct by a bleeding pseudocyst. In the fourth patient, who initially presented with colicky abdominal pain and intermittent melaena and in whom a recent ERCP had shown a dilated pancreatic duct with stones, the Wirsung duct was found at operation to be distended, full of blood and clots, and containing two stones. The largest quantity of haemorrhagic fluid aspirated from one pseudocyst was 2500 ml.

Intraperitoneal bleeding resulted from spontaneous rupture of the spleen in one patient who had splenic vein thrombosis and from intraperitoneal rupture of a bleeding distal pancreatic pseudocyst in a second patient who also had associated splenic vein occlusion. Severe compression of the splenic vein was also noted at operation in a third patient. None of the three patients with splenic vein occlusion had evidence of gastrointestinal varices.

Operative management

Urgent operation. The decision to undertake urgent surgery was made in six patients because of severe haemorrhage

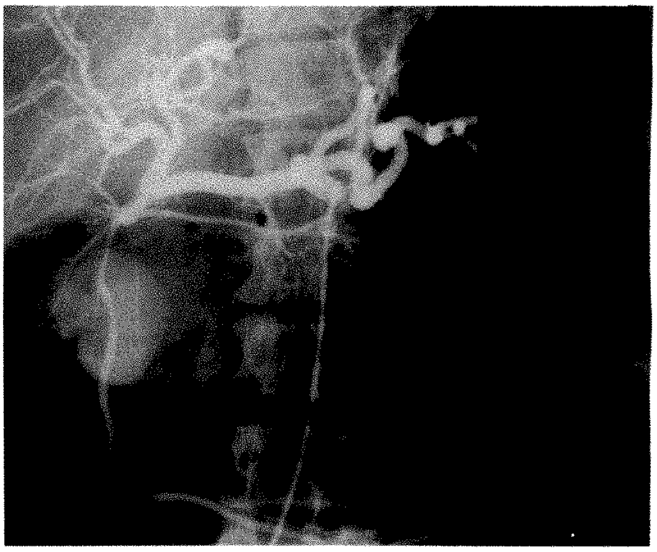

Figure 1 *Selective coeliac arteriogram showing a pseudoaneurysm originating from gastroduodenal artery. Arrows show normal pancreatic arteries*

Table 1 *Details of six patients with severe haemorrhage*

Patient no.*	Age/sex	Pancreatic pathology	Arteriography findings	Site of bleeding	Operative procedure	Outcome
1	51/F	Alcoholic calcific chronic pancreatitis		Spleen (peritoneal cavity)	Splenectomy	Diabetic lost to follow-up 7 years later
2	52/M	Alcoholic chronic pancreatitis. Pseudocyst. Previous laparotomy	Ruptured gastroduodenal artery pseudoaneurysm	Pseudocyst (duodenum)	Proximal pancreatic resection	Died 1 year later from alcoholism
3	34/M	Alcoholic chronic pancreatitis. Pseudocyst. Previous cholecystectomy	Splenic vein occlusion	Pseudocyst (peritoneal cavity)	1. Distal resection + splenectomy 2. Gastrostomy. External drainage	Reoperation for subphrenic abscess. Lost to follow-up 3 months later
4	32/F	Alcoholic chronic pancreatitis. Cirrhosis	Displacement/compression of common bile duct gastroduodenal artery and superior mesenteric vein	Pseudocyst (duodenum)	1. Transcystic arterial ligation. External drainage 2. Feeding jejunostomy	Reoperation for bleeding. Died 4th postoperative day from severe intra-abdominal sepsis
5	29/M	Alcoholic calcific chronic pancreatitis	Ruptured gastroduodenal artery pseudoaneurysm	Pseudocyst (duodenum)	1. Gastroduodenal artery ligation pseudocyst-duodenostomy 2. Proximal pancreatic resection	Reoperation for bleeding. Died 10 years later, liver cirrhosis
6	53/M	Chronic pancreatitis – unknown aetiology. Cirrhosis	Portal hypertension	Pseudocyst	1. Transcystic arterial ligation. Internal drainage	Died from septicaemia and hepatorenal syndrome (2nd postoperative day)

Table 2 *Clinical details of 11 patients with intermittent or intracystic haemorrhage*

Patient no.	Age/sex	Pancreatic findings	Arteriogram findings	Site of bleeding	Operative procedure	Outcome
1	42/M	Chronic pancreatitis of unknown aetiology + pseudocyst		Pseudocyst (Wirsung duct)	Proximal pancreatic resection	Diabetic, alive at 8 years
2	42/M	Chronic pancreatitis of unknown aetiology. Pseudocysts + gastric ulcer		Pseudocyst (duodenum)	1. Proximal pancreatic resection 2. External drainage	Reoperation for sepsis. Anastomotic ulcer, (vagotomy). Diabetes. Alive at 12 years
3	48/M	Alcoholic chronic pancreatitis. Pseudocysts	Gastroduodenal artery pseudoaneurysm (peroperative cystography)	Pseudocyst (Wirsung duct)	Proximal pancreatic resection	Bile fistula. Aggravation of diabetes. Anastomotic ulceration. Alive at 7 years
4	50/M	Alcoholic chronic pancreatitis. Previous cholecystectomy		Pseudocyst	Proximal pancreatic resection	Asymptomatic at 6 years
5	41/M	Alcoholic chronic pancreatitis. Pseudocysts. Cirrhosis		Pseudocyst (Wirsung duct)	Proximal pancreatic resection	Pancreatic fistula, symptomatic. Lost to follow-up after 7 years
6	47/M	Alcoholic chronic pancreatitis. Pseudocyst. Cirrhosis	Compression of superior mesenteric artery	Pseudocyst	Proximal pancreatic resection	Symptomatic. Lost to follow-up after 3 years
7	41/M	Alcoholic chronic pancreatitis. Pseudocysts		Pseudocyst (duodenum)	Proximal pancreatic resection	Anastomotic ulcer, splenomegaly, hypersplenism. Splenectomy 3 years later
8	47/M	Calcific chronic pancreatitis, unknown aetiology. Pseudocyst	Ruptured splenic artery pseudoaneurysm	Pseudocyst	Distal pancreatic resection + splenectomy	Diabetic at 3 years
9	54/M	Alcoholic calcific chronic pancreatitis	Normal	Wirsung duct	Pancreaticojejunostomy	Lost to follow-up after 3 months
10	44/M	Alcoholic chronic pancreatitis. Pseudocysts		Pseudocyst	1. Transcystic arterial ligation + cystjejunostomy 2. External drainage	Reoperation for bleeding bile duodenal fistula. Cholecystectomy 4 years later. Diabetes
11	50/F	Calcific chronic pancreatitis. Pseudocysts		Pseudocysts	1. Transcystic arterial ligation. Cystgastrostomy 2. External drainage	Asymptomatic at 6 years follow-up

(*Table 1*). Splenectomy was carried out in a diabetic patient who had a ruptured spleen in association with splenic vein thrombosis. Control of bleeding into the duodenum from a ruptured gastroduodenal artery pseudoaneurysm in one patient and of intra-abdominal bleeding from intraperitoneal rupture of a distal pseudocyst associated with splenic vein occlusion in a second patient was achieved by primary pancreatic resection. A postoperative subphrenic abscess needed surgical drainage in the latter patient. Suture ligation of the accessible bleeding vessels in combination with external drainage of a pseudocyst was carried out in two jaundiced and cirrhotic patients. Both patients died after surgery, one from hepatorenal failure and generalized sepsis and the other from anastomotic failure after secondary proximal pancreatic resection carried out for rebleeding. Proximal ligation of the gastroduodenal artery and transcystic suture in combination with cystduodenostomy, after widening of a pre-existing pseudocystduodenal communication, was carried out in a sixth patient who had a ruptured gastroduodenal artery pseudoaneurysm and compression of the portal vein. A salvage proximal pancreatectomy had to be carried out in this patient for severe bleeding on the second postoperative day.

Early operation. In 11 patients (*Table 2*) who presented with intermittent bleeding, operation was undertaken on a semi-urgent basis. Proximal pancreatic resection was carried out in seven patients for bleeding pseudocysts located in the pancreatic head. Rupture into the duodenum was seen in two patients and into the pancreatic duct in three. In one of the latter group of three patients a pseudoaneurysm of the gastroduodenal artery had ruptured into a pseudocyst which in turn communicated with the Wirsung duct. Distal pancreatectomy was performed for a pulsatile and expanding abdominal mass resulting from rupture of the splenic artery into a pseudocyst. Lateral pancreaticojejunostomy was carried out in one patient for pancreatic duct bleeding secondary to pancreatic lithiasis. Cystgastrostomy and cystjejunostomy with intracystic suturing of bleeding vessels in combination with external drainage were carried out in two patients with multiple pseudocysts affecting the head and tail of the gland. There were no postoperative deaths in this group. Postoperative bleeding occurred in the patient treated by a cystjejunostomy which was controlled at a second operation by local suturing and external drainage after dismantling the anastomosis. His recovery was delayed by a duodenal fistula. He became diabetic and underwent cholecystectomy for gallstones 4 years later. Of the eight patients treated by primary pancreatic resection, two had transient postoperative bile or pancreatic fistulae and a third had surgical drainage of an intra-abdominal collection. Four patients suffered one or more late complications. One of three patients who developed anastomotic ulcers 3–12 months after the operation had an episode of haematemesis from his ulcer and was subsequently treated by transthoracic vagotomy. A second patient with anastomotic ulcer, who was found at operation to have occlusion of the splenic vein, presented 5 years later with splenomegaly and hypersplenism but had no evidence of gastrointestinal varices. He was treated by splenectomy. Insulin-dependent diabetes developed in two patients and was aggravated in a third.

Outcome

The mortality rate in this series was 12 per cent overall and 33 per cent following urgent operation. Of the 15 patients with bleeding pseudocysts and pseudoaneurysms, early postoperative complications developed in four of the ten who underwent primary pancreatic resection and in four of the five patients who had bleeding controlled by ligation and drainage. Complications were also more serious (three episodes of rebleeding) in those patients who did not have primary pancreatic resection. Early reoperation was required in five patients (33 per cent). Three reinterventions were carried out for postoperative intracystic bleeding in three patients initially treated by non-resectional procedures. Proximal pancreatic resection was carried out as a second operation for the control of rebleeding in two patients, one of whom died.

Discussion

Chronic pancreatitis and associated pseudocysts can lead to the life-threatening complication of pseudoaneurysm formation, splenic vein thrombosis and, much less frequently, infarction-rupture of the spleen. Isolated splenic vein thrombosis with or without segmental portal hypertension is reported in 5–37 per cent of patients with chronic pancreatitis[6,10,11], while erosion and/or aneurysmal degeneration of vessels adjacent to the pancreas has been reported in 10 per cent[12]. Duration of the disease and the presence of splenic vein thrombosis were found to be significant predictors of pseudoaneurysm[13]. The splenic artery is the vessel most commonly affected by a pseudoaneurysm but other visceral arteries may be weakened by the digestive action of pancreatic enzymes[12].

Haemorrhage from a ruptured pseudoaneurysm occurs into various parts of the gastrointestinal tract, the peritoneal cavity or retroperitoneum[3,9,14]. Bleeding through the papilla of Vater following erosion of a pseudocyst or rupture of a pseudoaneurysm into the pancreatic duct has also been described[15–17]. Pancreatic duct bleeding may follow ulceration and erosion of vessels or perforation of the Wirsung duct as a result of pancreatic lithiasis, but this is a rare complication of chronic pancreatitis[18]. Bleeding can be vigorous with rapid development of shock, requiring urgent operative intervention to identify the source of bleeding. In other instances the urgency of the condition becomes apparent only if the bleeding continues or occurs repeatedly in patients who have exhibited only mild clinical symptoms. Thus the diagnosis may be overlooked at initial evaluation, only becoming apparent after repeated hospital admissions and unsuccessful operative procedures[19]. To facilitate early and precise diagnosis abdominal ultrasonography, CT scan and visceral angiography, in a complementary capacity, should be considered. Identification of the site of bleeding at laparotomy may be exceedingly difficult making preoperative detection of the bleeding source desirable. Peripancreatic vascular lesions can be identified by angiography, and in selected cases the risk of urgent operation to control massive haemorrhage may be obviated by embolization[20,21] though this was not undertaken in the present series.

The two surgical options are resection of the affected pancreatic segment or arterial ligation in combination with external or internal drainage of coexisting pseudocysts. The reported operative mortality rate in collected series varies between 12 and 50 per cent, according to the patient's clinical state, the site and nature of the bleeding lesion and the timing of operation[1–3,9]. Operative mortality rates from bleeding lesions in the head of the pancreas are higher than those associated with lesions located in the region of the tail. Postoperative haemorrhage and sepsis were the main causes of death.

In this series spontaneous haemorrhage related to the pancreas developed in 10 per cent of our patients with chronic pancreatitis, most of whom were alcoholics with severe underlying pancreatic disease and pseudocyst formation. Preoperative visceral angiography in eight patients and intraoperative pseudocystography in one patient identified arterial and venous complications in a similar pattern to that previously reported[23]. Haemorrhage into a pseudocyst was achieved when operative strategy could be directed towards control of bleeding and removal of the affected pancreatic segment. Transcystic ligation and drainage for bleeding pseudocysts was associated with a high complication rate (four of five treated patients). Transcystic suture ligation of bleeding vessels and external pseudocyst drainage is attended by a high rebleeding and reintervention rate, but proximal and distal ligation of the bleeding artery as an adjunctive measure may be more successful[1,24,25]. Control of bleeding by suture ligation can be inadequate or even not technically possible in deeply located cysts and is unlikely in the presence of peripancreatic inflammation[26]. Pancreatic resection of haemorrhagic pseudocysts located in the head or tail of the pancreas, especially with perforation into the duodenum or the Wirsung duct, constituted an effective and definitive treatment in two-thirds of our patients. Our early postoperative complication rate was higher than that seen in our experience of elective operation for chronic pancreatitis[27] but the late results are not dissimilar except for the high incidence of anastomotic ulceration (three of nine patients). It is worth noting that splenectomy for splenomegaly and hypersplenism was carried out in one patient in whom the diagnosis of splenic vein occlusion was made at his initial operation 5 years earlier.

In summary, haemorrhage is a potentially life-threatening event during the course of chronic pancreatitis. Operation in the presence of haemorrhage is difficult and carries an increased operative risk and postoperative complication rate. These risks are even greater in the presence of compromised liver function or reintervention for postoperative bleeding. Appropriate surgical management has to be individualized. Favourable results can be accomplished by primary pancreatic resection which should be the recommended treatment whenever possible for bleeding pancreatic pseudocysts and pseudoaneurysms.

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References

1. Gadacz TR, Trunkey D, Kieffer RF. Visceral vessel erosion associated with pancreatitis. *Arch Surg* 1978; **113**: 1438–40.
2. Wolstenholme JT. Major gastrointestinal haemorrhage associated with pancreatic pseudocysts. *Am J Surg* 1974; **127**: 377–81.
3. Eckhauser FE, Stanley JC, Zelenock GB *et al.* Gastroduodenal and pancreaticoduodenal artery pseudoaneurysms: a complication of pancreatitis causing spontaneous gastrointestinal haemorrhage. *Surgery* 1980; **88**: 335–44.
4. Starling JR, Crummy AB. Hemosuccus pancreaticus secondary to ruptured splenic artery pseudoaneurysm. *Dig Dis Sci* 1979; **24**: 726–9.
5. Fekete F, Laigneau P, Belghiti J. Les haemorrhagies digestives au cours des pancreatites chroniques. *Gastroenterol Clin Biol* 1980; **4**: 551–5.
6. Leger L, Lenriot JP, Lemaigre G. L'hypertension et la stase portale segmentaire dans les pancreatites chroniques. A propos de 126 cas examines par splenoportographie et splenomanometrie. *J Chir* 1968; **95**: 599–608.
7. Jost JL, Hureau J, Vayre P. Quatre observations inedites d'infarctus veineux splenique au cours des atteintes pancreatiques chroniques. *J Chir* 1978; **115**: 337–44.
8. Malafosse M, Gallot R. Complications haemorrhagiques des pancreatites chroniques. *Ann Chir* 1976; **30**: 833–5.

9. Stabile BE, Wilson SE, Debas HT. Reduced mortality from bleeding pseudocysts and pseudoaneurysms caused by pancreatitis. *Arch Surg* 1983; **118**: 45–
10. Rosch J. Die Splenoportographie in der Diagnostik der Pankreas erkrankigen. *Der Radiologie* 1965; **5**: 274–81.
11. Tylen U, Arnesjo B. Angiographic diagnosis of inflammatory disease of the pancreas. *Acta Radiol Diagn* 1973; **14**: 215–40.
12. White AF, Baum S, Barabasiri S. Aneurysms secondary to pancreatitis. *AJR* 1976; **127**: 393–6.
13. Hofer BO, Ryan JA, Freeny PC. Surgical significance of vascular changes in chronic pancreatitis. *Surg Gynecol Obstet* 1987; **164**: 499–505.
14. Bucknam C. Arterial haemorrhage in a pseudocyst of the pancreas. *Arch Surg* 1966; **92**: 405–6.
15. Dagradi AE, Melster L. Massive upper gastrointestinal bleeding originating in the pancreas. *Gastroenterology* 1959; **36**: 269–72.
16. Sandblom P. Gastrointestinal haemorrhage through the pancreatic duct. *Ann Surg* 1970; **171**: 61–6.
17. Vankemmel M, Paris JC, L'Hermine C, Houcke M. Les wirsungorragies: étude de 6 cas personels et revue de la literature. *Med Chir Dig* 1976; **5**: 83–91.
18. Marescaux J, Evrard S, Aprahamian M *et al.* Pancreatic lithiasis: a rare cause of gastrointestinal haemorrhage. *Surgery* 1989; **105**: 682–5.
19. Cahow CE, Gusberg RJ, Gottlieb LJ. Gastrointestinal haemorrhage from pseudoaneurysm in pancreatic pseudocysts. *Am J Surg* 1983; **145**: 534–41.
20. Huizinga WKJ, Kalideen JM, Bryer JV, Bell PSH, Baker LW. Control of major haemorrhage associated with pancreatic pseudocysts by transcatheter arterial embolization. *Br J Surg* 1984; **71**: 133–6.
21. Baker KS, Tisnado J, Cho SR, Beachley MC. Splanchnic artery aneurysms and pseudoaneurysms: transcatheter embolization. *Radiology* 1987; **163**: 135–9.
22. Crile G, Jaffe HL. Pancreatic calculi as a rare cause of intestinal haemorrhage. Report of a case. *Radiology* 1946; **46**: 586–9.
23. Woltman AC, Leurs PR, Athanasoulis CA, Warshaw AL. Massive arterial haemorrhage in patients with pancreatitis. *Arch Surg* 1986; **121**: 439–44.
24. Gogbill CL. Haemorrhage in pancreatic pseudocysts. *Ann Surg* 1968; **167**: 112–15.
25. Grenstein A, De Mario EF, Nasbeth DC. Acute haemorrhage associated with pancreatic pseudocysts. *Surgery* 1971; **69**: 56–62.
26. Frey CF, Child CG, Frey W. Pancreatectomy for chronic pancreatitis. *Ann Surg* 1976; **184**: 403–412.
27. Adda G, Parc R, Huguet C, Malafosse M, Loygue J. Traitement chirurgical des pancreatites chroniques. *Chir Visceral* 1983; **1**: 35–46.

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Pulmonary microvasculature in experimental acute haemorrhagic and oedematous pancreatitis

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The pulmonary microvasculature was examined in two experimental models of acute pancreatitis by scanning electron microscopy of microvascular corrosion casts. Haemorrhagic pancreatitis was induced in eight male Sprague–Dawley rats using an intraductal injection of 5 per cent sodium taurocholate. Oedematous pancreatitis was induced in seven male Spague–Dawley rats using an intravenous infusion of supramaximal doses of caerulein (5 µg/kg per hour). The pulmonary vessels were cast using a polymer resin and the cast studied by scanning electron microscopy at 3 and 12 h in those with haemorrhagic and at 1 and 4 h in those with oedematous pancreatitis. Vascular abnormalities were present in both models at the initial study time with abruptly terminating vessels being more prominent in the caerulein model. At the later times, however, the abnormalities in the sodium taurocholate model were much more severe, with a substantial loss of vascular density, tortuosity and abrupt terminations of those vessels present. Microvascular abnormalities may be responsible for some of the pulmonary changes seen in oedematous and haemorrhagic pancreatitis.

Acute lung injury is a major factor contributing to the mortality associated with acute pancreatitis. Sixty per cent of deaths occurring within the first 7 days are directly related to respiratory complications[1]. The severity of lung injury varies from relatively mild atelectasis to acute respiratory failure associated with adult respiratory distress syndrome[2].

This study examines the effect of experimental mild oedematous and severe haemorrhagic pancreatitis on the pulmonary microvasculature and attempts to elucidate the pathogenesis of lung injury.

Materials and methods

Haemorrhagic pancreatitis was induced in eight male Sprague–Dawley rats, weight range 350–450 g, by retrograde intraductal injection of 0·2 ml 5 per cent sodium taurocholate. Six control animals received a retrograde intraductal injection of 0·2 ml saline. Three control and four test animals each were killed 3 and 12 h after injection; in a previous study local microvascular changes were identified after bile salt injection[3] and 12 h were required for the pancreatitis to evolve fully[4].

Oedematous pancreatitis was induced in seven male Sprague–Dawley rats (weight range 350–450 g) by a 4-h intravenous infusion of supramaximal doses of caerulein (5 µg/kg per hour). Five control animals received an infusion of saline at the same rate. Two control and three test animals were killed after 1 h, and three control and three test animals were killed after 4 h. Local microvascular changes have been reported 1 h after commencing caerulein infusion[5]. The model requires at least 4 h to evolve fully[6].

Anaesthesia was induced by an intraperitoneal injection of chloral hydrate (36 mg/100 g), and was maintained throughout the observation period in those animals receiving the intravenous infusion of caerulein. At the end of each study time, laparotomy and thoracotomy were performed and the pancreas was biopsied before casting preparation began. The descending thoracic aorta was ligated and a ligature was placed in position around the trachea. The lungs were gently inflated until they filled the thoracic cavities and the trachea was then ligated. The left ventricle was cannulated using an 18 Fr Intramedicut cannula (Argyle, Sherwood Medical, Tullamore, Ireland) and an incision made in the right atrium to serve as an outflow channel. Retrograde perfusion of the lungs with normal saline (200 ml at hand pressure) was continued slowly until the lungs appeared white and the perfusate ran clear. The vessels were fixed by infusing 60 ml 2·5 per cent glutaraldehyde solution buffered to pH 7·0 at room temperature which remained *in situ* for 15 min. The lung vasculature was cast retrogradely using 5 ml of a methacrylate based medium, blue Mercox (Ladd Research Industries Incorporated, Burlington, USA)[7], which was infused slowly at hand pressure. As vascular filling occurred, the lung surface became blue. The cast lungs were left intact for 15 min (until the material hardened).

Lung biopsies were then performed and the organs were excised and placed in a water bath at 35°C for 2–3 h. The lungs were then completely immersed in a solution of 6 mol/l potassium hydroxide which was changed daily for 3–4 days until digestion of lung tissue was complete (confirmed by stereoscopic examination). The casts were then washed in a gentle stream of running water for 24 h, air dried, mounted on brass stubs using silver colloid, coated with gold in a Polaron E5100 sputter coater (Polaron Equipment Ltd., Watford, UK) using a standard technique[8] and scanned in a JOEL 35C scanning electron microscope (JOEL Ltd., Collingdale, London, UK) at an accelerating voltage of 15 kV[9].

Biopsies of the pancreas and lung were taken at each study time and were prepared for histological examination. All lung biopsies were taken from the middle lobes in all animals. Biopsies were also taken from the lower lobes of animals in the 12-h haemorrhagic pancreatitis model when the lung bases failed to perfuse. Paraffin sections, stained with haematoxylin and eosin, were examined by light microscopy.

Results

Acute haemorrhagic pancreatitis

Inflammation of the pancreas was obvious in all test animals. Moderate oedema of the gland and punctate haemorrhages were noted at 3 h; gross oedema, haemorrhagic inflammation, bile staining of the splenic tail, pancreatic ascites, fat necrosis and clinically obvious dehydration were noted after 12 h. Histologically, haemorrhagic pancreatitis was found in the test animals while the pancreas appeared normal in the controls. The entire lung surface of the animals killed after 3 h paled when perfused with saline and became blue on injection of Mercox. For those killed after 12 h, areas of the lung, particularly the lower lobes, remained pink regardless of the volume infused.

On scanning electron microscopy the pulmonary capillaries in the control animals were arranged in hexagonal rings and anastomosed to form basket-type structures which surrounded the alveolar sacs. The capillaries were uniform in size and did not taper or change in diameter with branching (*Figure 1a*). Capillaries constituted most of the vascular cast.

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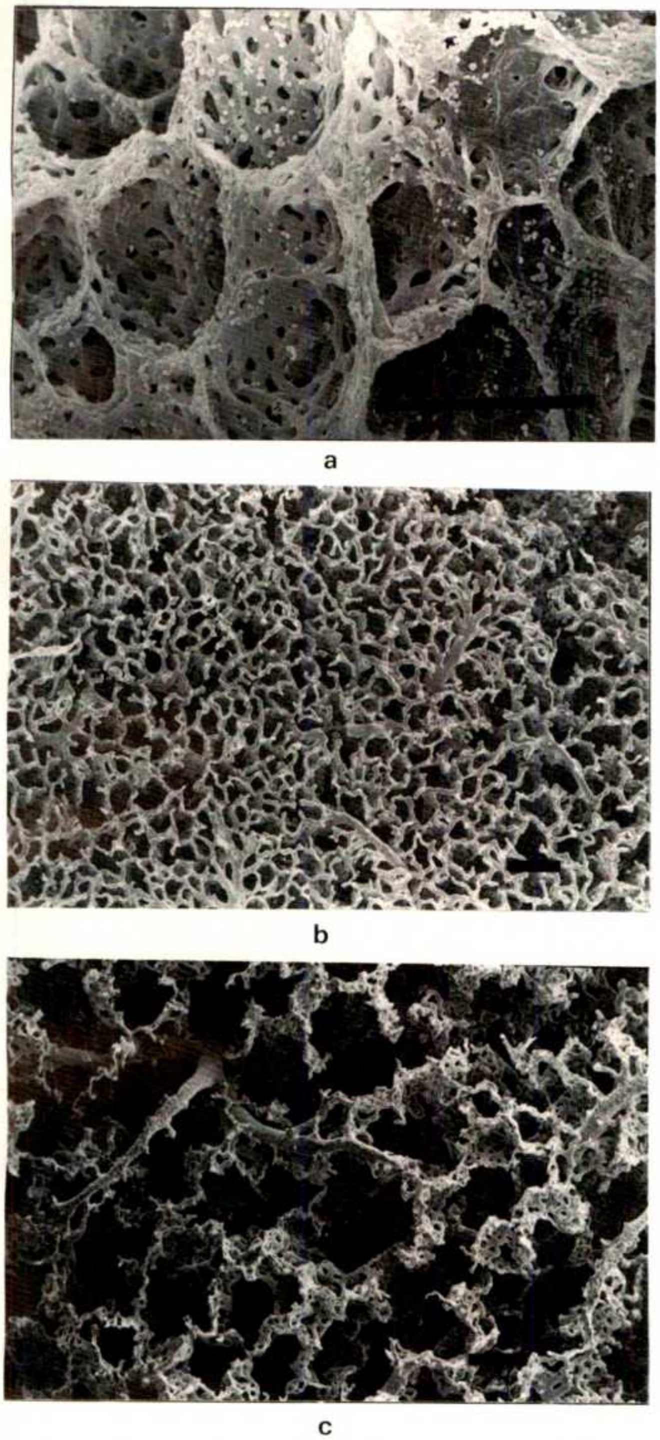

Figure 1 **a** *Scanning electron micrograph of the pulmonary vasculature. In the normal lung the capillaries, arranged in rings, form baskets around the alveoli.* **b** *Pancreatitis animal at 3 h: abruptly terminating vessels replace the organized ring structure and in some areas further fragmentation to the basic structure occurs (upper right).* **c** *A higher magnification view of the vasculature at 12 h in the pancreatitis animal reveals gross destruction of the normal vascular arrangement. The vessels are tortuous, end abruptly and bear no resemblance to those seen in the normal lung. (Bar, 100 μm)*

In test animals most of the pulmonary vasculature remained normal after 3 h; in some areas capillaries tapered or varied in size, but the overall density of vessels was within normal limits (*Figure 1b*). After 12 h there was a marked decrease in vascular density, which was clearly seen, even at low magnification. Some areas of normal capillary infrastructure could be found but these lungs were generally characterized by gross microvascular irregularity with disruption of basket-type capillary arrangement and tortuosity, tapering and abrupt terminations of the capillaries outlined (*Figure 1c*).

Histological examination of the lung at 3 h revealed vascular congestion as a prominent finding in all specimens. By 12 h, vascular congestion was accompanied by interstitial oedema, and macrophage and inflammatory cell infiltrate.

Oedematous pancreatitis

Pancreatitis was present in all experimental animals – mild hyperaemia was visible after 1 h and marked pancreatic oedema, together with a deep pink discoloration of the gland and accompanied by pancreatic ascites, was present after 4 h. The pancreas of control animals appeared normal both macroscopically and microscopically.

All areas of the lung perfused well at both time intervals in both the experimental and the control animals. Casts in the control animals revealed a normal pulmonary vascular arrangement (*Figure 2a*).

Vascular abnormalities were noted after 1 h in the experimental animals; the basket arrangement was incomplete in many instances, resulting in enlargement of the basic ring structure and abruptly terminating vessels. Many of the capillaries outlined were tortuous in appearance (*Figures 2b* and *c*). These areas were interspersed with normal pulmonary vasculature. At 4 h these abnormalities were accentuated and were found diffusely throughout the lung. The presence of abruptly terminating vessels was the most noticeable feature (*Figure 2d*). The overall loss of vascular density at low magnification was less than that seen in the haemorrhagic model.

Light microscopy at 1 h demonstrated areas of microvascular congestion; interstitial oedema with swelling of the interalveolar septum, combined with congested capillaries, was a prominent feature at 4 h. Microthrombi were not demonstrated in either model.

Discussion

The pathogenesis of pulmonary complications in acute pancreatitis remains unclear. Several factors have been implicated: mechanical, alteration in capillary permeability, and pulmonary microembolization. The spectrum of respiratory complications, many of which are characterized by local fluid retention, suggests that dysfunction at the alveolar/capillary membrane level is instrumental in their development[9,10]. Microvascular casting and scanning electron microscopy have been used to study the microvasculature of the pancreas in experimental caerulein-induced oedematous pancreatitis[5]. Using a similar technique, this study provides a detailed three-dimensional view of the pulmonary microcirculation in experimental oedematous and haemorrhagic pancreatitis. It confirms that microvascular distortion is not confined to the pancreas and occurs even in the relatively mild oedematous pancreatitis model.

The study times chosen for the two models took into account the time taken for each type of pancreatitis to evolve. The early changes were more marked in the oedematous pancreatitis model despite the fact that it is a reversible and less severe form of pancreatitis.

The microvascular disruption seen in both models may be due to a reduction in ventilatory excursion secondary to the intra-abdominal inflammatory process, especially in the haemorrhagic pancreatitis model where there was gross peripancreatic inflammation, pancreatic ascites and inadequate casting of the microvasculature in both lung bases probably due to basal atelectasis.

Altered capillary permeability may be a contributing factor[11,12], and recent work from this laboratory suggests that pancreatitis is associated with diffuse microvascular injury[5,13]. Interstitial oedema was clearly evident in both models on histological examination, suggesting increased capillary permeability. The microvascular appearances may be due to external compression by interstitial oedema. There was no evidence, however, of leakage of cast material from the vessel mould as previously demonstrated in the pancreas[5].

Altered coagulation is a recognized feature of severe forms of pancreatitis[14] but there was no evidence of intravascular thrombosis or embolism in either of these models.

The abnormalities demonstrated in both models were similar to changes demonstrated previously in the pancreas and liver in the caerulein model[5,13], supporting the concept that circulating toxins released from the inflamed pancreas are important in the pathogenesis of this diffuse microvascular injury. Guice *et al.*[14] provided evidence of increased pulmonary microvascular permeability in caerulein-induced pancreatitis, and suggested that oxygen free radicals may be responsible. Previous work from this laboratory supports a role for oxygen free radicals[15], while Schoenberrg *et al.*[16] recently demonstrated that free radical scavenger treatment after the onset of caerulein-induced pancreatitis may reduce local tissue damage.

This study helps to explain the pulmonary vascular derangement seen in acute pancreatitis and highlights the diffuse nature of the systemic microvascular injury. This injury may play a role in the development of the respiratory complications of acute pancreatitis.

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References

1. Cobo JC, Abraham E, Bland RD, Shoemaker WD. Sequential haemodynamic and oxygen transport abnormalities in patients with acute pancreatitis. *Surgery* 1984; **95**: 324–30.
2. Hayes MF, Rosenbaum RW, Zibelman M, Matsumoto T. Adult respiratory distress syndrome in association with acute pancreatitis. *Am J Surg* 1974; **127**: 314–19.
3. Kelly D, McEntee GP, McGeeney KF, Fitzpatrick JM. Extrapancreatic organ impairment in haemorrhagic pancreatitis is associated with systemic microvascular injury. *Ir J Med Sci* 1989; **158**: 236 (Abstract).
4. Aho HJ, Nevalainen TJ. Experimental pancreatitis in the rat: ultrastructure of sodium taurocholate induced pancreatic lesions. *Scand J Gastroenterol* 1980; **15**: 417–24.
5. McEntee GP, Leahy A, Cottell D, Dervan P, McGeeney KF, Fitzpatrick JM. Three dimensional morphological study of the pancreatic microvasculature in caerulein induced experimental pancreatitis. *Br J Surg* 1989; **76**: 853–5.
6. Tardini A, Anversa P, Bordi C. Ultrastructural and biochemical changes after marked caerulein stimulation of the exocrine pancreas in the dog. *Am J Pathol* 1971; **62**: 35–47.
7. Nelson AC. Study of the rat lung alveoli using corrosion casting and freeze fracture methods coupled with digital image analysis. *Scanning Electron Microscopy* 1987; **1**: 817–22.
8. Glauert AM. *Practical Methods in Electron Microscopy*. New York: Elsevier, 1974.
9. Hodde KC, Nowell JA. Scanning electron microscopy of micro-corrosion casts. *Scanning Electron Microscopy* 1980; **11**: 88–106.
10. Interiano B, Stuard D, Hyde RW. Acute respiratory distress syndrome in pancreatitis. *Ann Intern Med* 1972; **77**: 923–6.
11. Malik AB. Pulmonary oedema after pancreatitis: role of humoral factors. *Circ Shock* 1983; **10**: 71–80.

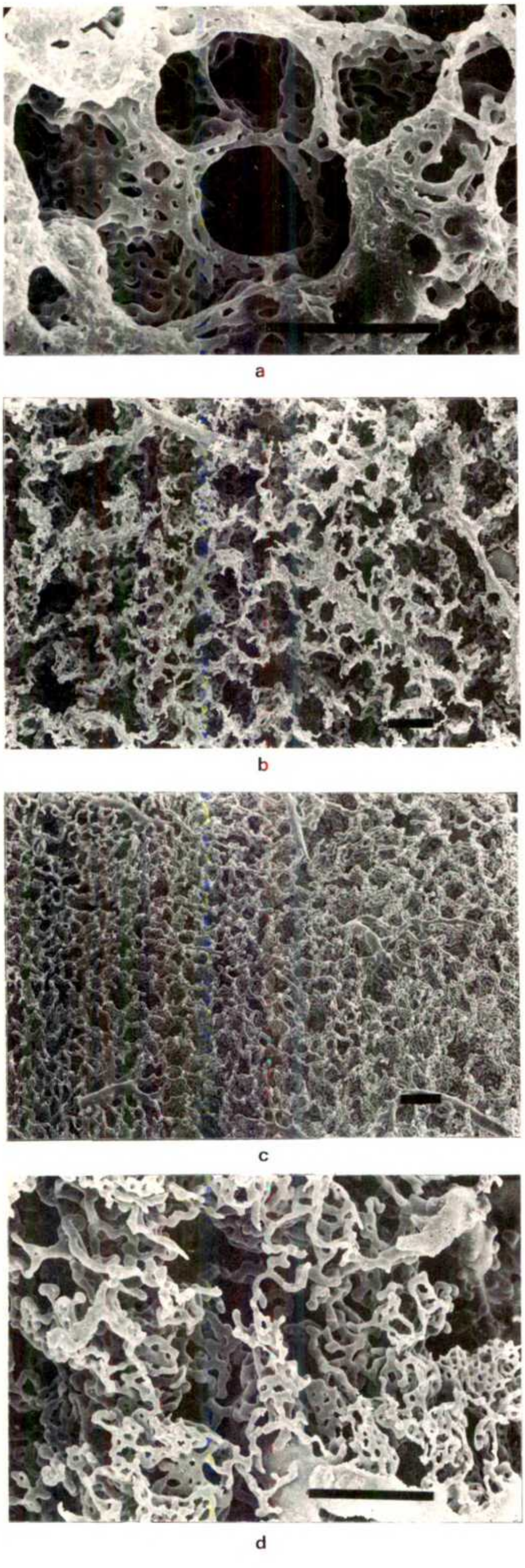

Figure 2 **a** *Scanning electron micrograph of the pulmonary vasculature in the control animal. The capillaries form a honeycomb structure. The hollow spaces were filled by the alveoli* in vivo. **b** *The pulmonary vasculature 1 h after induction of oedematous pancreatitis. The vascular density is relatively normal but the regular arrangement of vessels has been disrupted. Compare this with the appearance of the control gland at the same time point, as seen in* **c**. **d** *Pulmonary vasculature 4 h after induction of oedematous pancreatitis. The capillary baskets are no longer obvious as some of the capillaries fail to fill and end in branching structures rather than forming rings.* (*Bar, 100 μm*)

12. Tahamont MV, Barie PS, Blumenstock FA, Hussain MH, Malik AB. Increased lung vascular permeability after pancreatitis and trypsin infusion. *Am J Pathol* 1982; **109**: 15–26.
13. Delaney C, McEntee GP, Cottell D, O'Donnell MD, McGeeney KF, Fitzpatrick JM. The effect of caerulein induced pancreatitis on the hepatic microvasculature. *Br J Surg* 1990; **77**: 294–6.
14. Guice K, Oldham KT, Johnson KT, Kunkel RG, Morganroth ML, Ward PA. Pancreatitis induced acute lung injury. An ARDS model. *Ann Surg* 1988; **208**: 71–7.
15. Gough DB, Boyle B, Joyce WP *et al.* Free radical inhibition and serial chemiluminescence in evolving experimental pancreatitis. *Br J Surg* 1990; **7**: 1256–9.
16. Schoenberg MH, Buchler M, Gasper M *et al.* Oxygen derived free radicles in acute pancreatitis in the rat. *Gut* 1990; **31**: 1138–43.

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Spontaneous perforation of the bile duct in infants

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Spontaneous perforation of the bile duct is a rare but well documented condition of infants. Six infants are described, five presenting within 2 months of birth without apparent antecedent factors and one associated with an 'acquired' type I biliary atresia at 8 months. All infants underwent definitive surgery, which included decompression of the biliary tree with cholecystenterostomy or T tube drainage. There was no morbidity or mortality associated with such surgical intervention.

Since the first description by Dijkstra in 1932[1] approximately 70 cases of spontaneous perforation of the bile duct have been reported in infants. Many patients present with jaundice and biliary ascites within the first 2 months of life and at surgery are shown to have a perforation which is usually at the junction of the cystic and common bile ducts. Spontaneous perforation of the bile duct has been described as the second commonest cause of jaundice in infancy after extrahepatic biliary atresia[2,3]. Previous reports have described no more than two cases so that recommendations on ideal management have been based on limited personal experience.

Six patients presenting over a 16-year period, operated on by a single surgeon, are presented and suggestions for a definitive management plan are formulated.

Patients and methods

Six infants with spontaneous perforation of the biliary tract were managed by one surgeon (E.R.H.) during the period 1974–90 (two patients have been previously reported[4] and are included). All were investigated in a supraregional paediatric hepatobiliary centre receiving infants from the south of England.

Clinical data

There were three female patients and three males. There was no history of familial liver disease in any infant. One female infant was of a consanguineous marriage but five previous siblings were normal.

Five infants (*Table 1*, patients 1, 2, 4, 5, 6) presented at 2–12 weeks after normal gestation and delivery, and birth-weights and postnatal examinations were normal. One of these infants suffered a group D streptococcal septicaemia on the second day of life, treated with appropriate antibiotics. Only one of the five infants was not jaundiced on admission but presented with bilious vomiting, pale stools and abdominal tenderness. Two male infants had patent processus vaginales, with bile-stained hydroceles in one case and an inguinal hernia in the other. Ascites was clinically obvious in three of the infants but all were reasonably well on admission despite the confirmation of intraperitoneal bile at laparotomy.

One female infant born at 28 weeks' gestation weighing 800 g (*Table 1*, patient no. 3) had an atypical presentation and pathology. A complicated neonatal period included respiratory distress syndrome requiring ventilation, pneumothoraces, ligation of a patent ductus arteriosus and a prolonged period of parenteral nutrition. There was a prolonged period of neonatal jaundice which resolved before discharge. The patient re-presented at 8 months of age with a 3-week history of jaundice, acholic stools and failure to thrive.

Investigations

Preliminary investigations of the six infants revealed conjugated hyperbilirubinaemia and a raised alkaline phosphatase level (*Table 2*). Viral serology, complement and immunoglobulin levels in two cases were normal. Cytomegalovirus was isolated from the urine of infant no. 3 during the neonatal period. Ultrasonographic examination was always abnormal but never diagnostic (*Table 2*). Radionuclide scanning using di-isopropyliminodiacetic acid (DISIDA) was suggestive of perforation in one case but did not show excretion in the other. An ^{131}I-labelled rose bengal faecal excretion test was used in the two earliest patients and showed isotope excretion into ascites 12 h after administration.

Results

All infants underwent elective laparotomy after correction of vitamin K-dependent coagulation abnormalities. A large volume (up to 500 ml) of bile ascites was present in three infants. A chronic pseudocyst or inflammatory mass was always present in the region of the porta hepatis. Dissection always revealed a typical perforation at or near the junction of the cystic with the common hepatic duct. The size of the perforation varied from a 'pinhole' to a 4-mm defect. If dissection was difficult owing to chronic inflammatory tissue, 'on-table' cholangiography using a cholecystostomy catheter helped to define the biliary anatomy. Inspissated bile was thought to be the cause of distal bile duct obstruction, revealed by saline flushing or cholangiographic examination, in four of the five infants with non-atretic ducts. Infant no. 3 had a membranous type of acquired atresia of the distal common bile duct with a proximal pinhole perforation from which bile leaked into a cystic collection within the lesser sac.

Definitive surgical management was performed in all infants. The first two infants (patient nos. 1 and 2) in the series had a cholecystenterostomy-en-Roux and oversew of the perforation. The infant with acquired biliary atresia (patient no. 3) underwent local excision of the atretic segment and an end-to-end anastomosis of the common duct. One infant (patient no. 4), with the largest tear and almost complete disruption of the bile duct, had the distal residual duct excised and a hepaticojejunostomy-en-Roux. Cholecystectomy and latex T tube drainage (6 Fr) through the perforation were

Table 1 *Clinical features in six cases of spontaneous perforation of the biliary tract*

Patient no.	Sex	Perinatal period	Age at presentation (weeks)	Features
1	M	Uneventful	2	Jaundice, pale stool, vomiting, ascites
2	M	Uneventful	5	Jaundice, pale stool, inguinal hernia surgery, ascites
3	F	Premature, respiratory distress syndrome, ventilated	24	Jaundice, hepatomegaly, mass
4	M	Uneventful	2	Anicteric, pale stools, abdominal discomfort, low-grade pyrexia
5	F	Uneventful	12	Jaundice, gross ascites, umbilical hernia
6	F	Streptococcal septicaemia	2	Mild jaundice, bile vomit, mass

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Table 2 *Investigations in six cases of spontaneous perforation of the biliary tract*

	Biochemistry*					
Patient no.	Bilirubin (total) (μmol/l)	Alkaline phosphatase (units/l)	Aspartate aminotransferase (units/l)	γ-glutamyl transpeptidase (units/l)	Ultrasonography	Radionuclide scanning
1	156	350	183	—	—	Excretion into ascites (RB)
2	117	457	30	—	—	Excretion into ascites (RB)
3	285	1018	—	846	Mass, ?choledochal cyst	—
4	16	735	54	571	Complex, multicystic mass, ?duplication cyst	No excretion (^{99m}TcD)
5	53	585	—	222	Mass with visible septa	Excretion into ascites (^{99m}TcD)
6	52	376	35	—	Complex, multicystic mass, ?duplication cyst	—

*Normal range: bilirubin <20 μmol/l; alkaline phosphatase 30–110 units/l; asparate aminotransferase 10–50 units/l; γ-glutamyl transpeptidase 5–55 units/l. RB, ^{131}I-labelled rose bengal excretion; ^{99m}TcD, ^{99m}Tc-labelled di-isopropyliminodiacetic acid

performed in the last two infants (patient nos. 5 and 6). The gallbladder was retained in only the first two infants (patient nos. 1 and 2).

Postoperative recovery was uneventful with rapid resolution of jaundice in all cases. T tubes were left *in situ* for 14 days and removed after cholangiographic confirmation of free distal flow into the duodenum. All patients were followed for at least 1 year and remained jaundice free. They have been followed with annual review and have had no episodes of cholangitis nor any other complication. Infant no. 3 (acquired atresia) had percutaneous transhepatic cholangiography 1 year after surgery which showed a normal biliary tree with no evidence of stricture. She is without evidence of chronic liver disease and has normal biochemical liver function tests 4 years after surgery.

Discussion

It is not possible to define the incidence of spontaneous perforation of the bile duct accurately. During the period in which these patients were treated, 15 infants with choledochal cyst and more than 250 infants with extrahepatic biliary atresia have been treated, suggesting that the condition is less common than has been previously suggested.

This series complements previous descriptions of the clinical features in spontaneous perforation of the bile duct and illustrates the usual chronic presentation with jaundice and abdominal swelling due to ascites[5]. An acute presentation has been recorded occasionally[6]. Abdominal hernias and hydroceles occur, presumably due to ascites and increased intra-abdominal pressure. The perforations in the present series were misdiagnosed using ultrasonography because of the formation of a mass around the common bile duct. This appearance, however, with the presence of free intraperitoneal fluid, should point to the correct diagnosis. Abnormalities on radionuclide scanning depend on whether an obstructive element is present. The ^{131}I rose bengal faecal excretion test[4] is no longer used because of difficulties inherent in sample collection, and scanning with ^{99m}Tc-labelled di-isopropyliminodiacetic acid is currently used. The key to correct diagnosis is still based on accurate history and examination. In contrast with previous reports[2,7], all of our jaundiced infants had raised alkaline phosphatase and γ-glutamyl transpeptidase levels in keeping with the dilatation of the intrahepatic biliary radicals visualized on ultrasonography.

The patient with acquired biliary atresia (case no. 3) contrasts with those with congenital biliary atresia in the relatively late presentation and the rapid return of normal liver function after operation. The prognosis in congenital biliary atresia treated at 24 weeks is extremely poor and liver function tests would not return to normal even if biliary drainage were achieved. The acquired occlusion of the common bile duct was probably a result of the sclerosing effect of the bile leak from the perforation.

No common aetiological factor has been identified for the perforations, but the proximity of the defect to the junction of the cystic duct does support the theory of an embryological mural weakness first postulated by Pettersson in 1955[8] and later by Johnston in 1961[9]. What precedes the presumed rise in duct pressure remains speculative. Inspissated bile obstruction may have been a factor in four of our infants and this feature has been commented on by others[1,10]. Associated cysts or sacs in the region of the cystic duct were noted by some[11] but were probably a result of bile leakage rather than the cause. The perforations do seem to be 'punched out' local defects. The subsequent leak of bile forms a limited collection around the common bile duct, into the lesser sac and peritoneal cavity.

A viral aetiology was suspected by Moore but without any substantive evidence[12]. There were no abnormal viral titres or immunoglobulin levels in the six patients, although cytomegalovirus was isolated from the urine of a very premature neonate. Mechanical obstruction to bile flow is a more likely cause of the perforations.

All reports of conservative management have ended with the death of the child. Each surgeon's experience is limited by the rarity of the condition and dogmatic statements on treatment are inappropriate. Simple peritoneal toilet and drainage[2,3] has been suggested, but deaths have been recorded with this technique[2]. Primary suture of the perforation with peritoneal drainage has also been reported as satisfactory[13].

Any method of treatment must include a check for patency and flow into the duodenum either by flushing with saline or with radio-opaque contrast via a catheter placed in the gallbladder. Obstruction of the distal common bile duct has been observed in several of the reported patients[2,4]. The principle of operative management should be decompression of the biliary tree to allow prompt healing of the perforation. This was achieved earlier in the series by cholecystenterostomy, and has been used with success by other authors[14]. Concern about possible long-term complications of this procedure suggested the formation of a controlled external fistula using a small latex T tube (6 Fr) inserted at the site of perforation. Cholecystectomy was necessary in the two cases treated in this manner because the perforation had compromised the junction of the cystic duct with the common hepatic duct. This latter technique, which has been used before[15], was satisfactory and radiological confirmation of distal flow in the postoperative period was helpful. There were no later complications such as stricture formation or persistent fistula with this method of treatment.

References

1. Dijkstra CH. Graluistorting in de buikholte bij een zuigeling. *Maandschr Kindegeneeskd* 1932; **1**: 409–14.
2. Lilly JR, Weintraub WH, Altman RP. Spontaneous perforation of the extrahepatic bile ducts and bile peritonitis in infancy. *Surgery* 1974; **75**: 664–73.
3. Hammoudi SM, Alauddin A. Idiopathic perforation of the biliary tract in infancy and childhood. *J Pediatr Surg* 1988; **23**: 185–7.
4. Howard ER, Johnston DI, Mowat A. Spontaneous perforation of common bile duct in infants. *Arch Dis Child* 1976; **51**: 883–6.
5. Hyde GA. Spontaneous perforation of bile ducts in early infancy. *Pediatrics* 1965; **35**: 453–7.
6. Stringal G, Mercer S. Idiopathic perforation of the biliary tract in infancy. *J Pediatr Surg* 1983; **18**: 546–50.
7. Lees W, Mitchell JE. Bile peritonitis in infancy. *Arch Dis Child* 1966; **41**: 188–92.
8. Pettersson G. Spontaneous perforation of the common bile duct in infants. *Acta Chir Scand* 1955; **60**: 192–201.
9. Johnston JH. Spontaneous perforation of the common bile-ducts in infancy. *Br J Surg* 1961; **48**: 532–3.
10. Caulfield E. Bile peritonitis in infancy. *Am J Dis Child* 1936; **52**: 1348–60.
11. Byrne JJ, Bottomley GT. Bile peritonitis in infancy. *Am J Dis Child* 1953; **85**: 694–7.
12. Moore TC. Massive bile peritonitis in infancy due to spontaneous bile duct perforation with portal vein occlusion. *J Pediatr Surg* 1975; **10**: 537–8.
13. Enell H, Cavell B, Malmfors G. Spontaneous perforation of the common bile duct. *Acta Paediatr Scand* 1979; **68**: 625–6.
14. Fitzgerald RJ, Parbhoo K, Guiney EJ. Spontaneous perforation of bile ducts in neonates. *Surgery* 1978; **83**: 303–5.
15. Wright JP, Worsley HE. A case of rupture of the hepatic duct in a newborn infant. *Arch Dis Child* 1959; **34**: 277–8.

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Surgical restraint in the management of liver trauma

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Previous experience in Cambridge in the management of liver trauma has led to the evolution of a protocol for surgical intervention to secure control of haemorrhage from the injured liver. We report 80 cases of liver trauma including 12 who were initially managed non-operatively; three of these subsequently required operation. Of the 80, all but five suffered blunt abdominal trauma. Perihepatic packing was used to manage 29 patients, of whom 21 were initially treated elsewhere before being transferred to Cambridge. Six of these required a hemihepatectomy at subsequent exploration. Of the 39 patients who underwent urgent laparotomy and definitive surgery, 11 (28 per cent) died; only three out of 29 (10 per cent) died after initial packing. Only one death from hepatic complications occurred after packing and subsequent transfer.

The management of liver trauma has been the subject of controversy for many years, with opinion divided between immediate aggressive surgery and surgical restraint. In the UK, where district hospitals do not admit large numbers of patients with liver trauma, and where anaesthetic and blood bank support may be limited, a more restrained surgical approach is appropriate. Most patients have blunt injuries which carry a worse prognosis than penetrating injuries. This contrasts with American experience where penetrating injuries are more common (for example 75 per cent of hepatic injuries admitted to the Ben Taub General Hospital, Houston, Texas between 1978 and 1985 were penetrating injuries)[1].

This paper reviews our experience over the last 20 years in a district general hospital with a major interest in hepatic surgery, with particular reference to the last 9 years' experience since the advent of computed tomography (CT) scanning into our practice in 1981. A policy of judicious packing and CT-based non-operative management has been practised in this high-risk group of patients.

Patients and methods

The case records of those patients admitted with liver trauma and undergoing surgery and/or CT scanning in the last 10 years were reviewed and the results correlated with the experience over the previous decade. The extent of the hepatic trauma was graded according to the surgical classification of Calne *et al.*[2] (*Table 1*). CT images were retrospectively reviewed by two authors (A.K.D., A.R.P.) and graded according to the radiological classification of Mirvis *et al.*[3] (*Table 2*); CT examinations were performed on one of two machines, a Siemens Somatom II (Siemens, Sunbury-on-Thames, UK) or a General Electric 9000 system (IGE Medical Systems, Slough, UK).

Results

Eighty patients who experienced severe hepatic trauma (Calne grade II or worse) between 1971 and 1990 were reviewed. *Table 3* shows the distribution of these patients by grade of injury. Twelve patients had evidence of significant hepatic trauma on CT scanning (Mirvis grade 2 or worse) and were managed non-operatively in the first instance. The aetiology of the injuries is given in *Table 4* – only five patients (6 per cent) had penetrating injuries (three stabbings, two gunshot wounds), the remainder experiencing blunt trauma. *Table 5* shows the numbers of patients with additional major injuries. The spleen was the most common solid organ injured (15 cases, 19 per cent), and significant chest injuries occurred in 26 (33 per cent) cases.

Grade II (Figure 1)

There were 20 patients with Grade II hepatic injuries. All were treated by simple suture, while four required additional splenectomy and two underwent thoracotomy for associated chest trauma. Two patients died, both at the time of surgery.

Table 1 *Surgical grading of hepatic trauma*

Grade I	Capsular tear, no parenchymal damage. Minor bleeding which stops spontaneously or with a few simple sutures.
Grade II	Parenchymal damage. Careful suturing secures haemostasis.
Grade III	Parenchymal damage. Major haemorrhage from intrahepatic arteries or veins threatening life/producing shock.
Grade IV	Parenchymal damage. Tear of inferior vena cava or major hepatic vessels.

After Calne *et al.*[2]

Table 2 *Computed tomographic scan grading of hepatic trauma*

Grade 1	Capsular avulsion; superficial laceration < 1 cm deep. Subcapsular haematoma of < 1 cm maximum thickness. Periportal blood tracking only.
Grade 2	Lacerations 1–3 cm deep. Central/subcapsular haematoma 1–3 cm diameter.
Grade 3	Lacerations > 3 cm deep. Central/subcapsular haematoma > 3 cm diameter.
Grade 4	Massive central/subcapsular haematoma > 10 cm. Lobar tissue destruction (maceration) or devascularization.
Grade 5	Bilobar tissue destruction (maceration) or devascularization.

After Mirvis *et al.*[3]

Table 3 *Distribution of 80 patients with different grades of injury*

Grade of injury	Number of patients	Age (years) Median	Range	Transfers	Deaths
II	20	19	6–59	0	2
III	24	21	11–43	12	3
IV	24	21	5–72	10	9
CT	12	28	12–71	2	0

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Table 4 *Aetiology of hepatic injury in 80 patients*

	Grade II	Grade III	Grade IV	Non-operative	Total
Car	13	8	7	5	33
Cycle/motorbike	3	9	10	2	24
Sport	0	2	0	1	3
Stab	2	1	0	0	3
Shotgun	0	0	2	0	2
Horse	0	0	1	2	3
Other	2	4	4	2	12

Table 5 *Numbers of patients with additional major injuries*

	Grade II	Grade III	Grade IV	Non-operative	Total
Head*	6	6	2	1	15
Chest†	4	5	14	3	26
Diaphragm rupture	1	3	1	0	5
Spleen‡	4	7	4	0	15
Other intra-abdominal injury§	2	3	3	4	12
Long bone fracture	5	6	3	3	17

* Head injuries refer to vault fractures or intracranial haemorrhage. † Chest injuries include flail chest, and haemothoraces and pneumothoraces requiring drainage. ‡ Splenic injuries are lacerations requiring splenectomy. § Other intra-abdominal injuries exclude hepatic and splenic injuries and refer to pancreatic transection, duodenal perforation and renal tract trauma

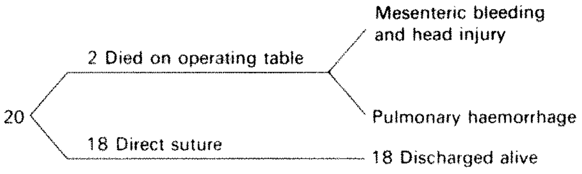
20
2 Died on operating table
Mesenteric bleeding and head injury
Pulmonary haemorrhage
18 Direct suture
18 Discharged alive

Figure 1 *Patients with Grade II trauma*

One had uncontrollable pulmonary haemorrhage, the other uncontrollable bleeding from multiple mesenteric tears in addition to a head injury and compound femoral fracture. Both developed a coagulopathy and suffered a hypovolaemic cardiac arrest on the operating table. The remaining 18 patients were discharged alive, all with good liver function.

Grade III (Figure 2)

Twenty-four patients were admitted with grade III trauma. Twelve had been transferred after primary treatment elsewhere, of whom 10 had packs *in situ*. Five other patients were treated by packing. Packing was the primary treatment in 12 of these 15 patients. In the other three patients packing was employed at a second procedure. In the first of these the liver was initially sutured, but continued blood loss necessitated a laparotomy later the same day, at which an area of devitalized liver was resected and the defect packed. The second patient had a splenectomy as a first procedure but in the face of continued blood loss a second laparotomy was performed. At this laparotomy the capsule over the right hepatic lobe was found to have been stripped off by an advancing haematoma, and this area was packed. It is probable that this represented an intrahepatic haematoma which enlarged, reached the capsule and separated it from the underlying parenchyma. This second patient had the packs changed 48 h later, before complete removal 4 days after initial admission. The third patient had a stab wound to the liver, which was initially treated by simple suture, but in the face of continued bleeding a second laparotomy was performed 24 h later at which the liver was packed. The patient was transferred to Addenbrooke's hospital and was re-explored, when a central haematoma was deroofed.

Two patients in this group died during their first operation: one from a major head injury, the other from massive facial haemorrhage associated with head, chest and lower limb injuries. A third patient died at a second laparotomy. He had presented with a stellate rupture of the right lobe of the liver, a ruptured spleen, and a subdural haematoma requiring decompression with burr holes. His liver rupture was sutured and packed. However, he continued to bleed and was reoperated upon but died in spite of repacking and hepatic artery ligation. Of the 24 patients four were examined by CT scanning before operation, with the liver injury radiologically graded 3 or 4 (*Table 6*). There was no significant morbidity relating to the hepatic injury in either grade II or grade III other than that mentioned already.

Grade IV (Figure 3)

Twenty-four patients with grade IV trauma were treated. Nine died, seven at the time of surgery and an eighth 12 days later from a cardiac arrest compounded by a major head injury and flail chest. Of the seven who died at the time of surgery, one suffered a hypovolaemic cardiac arrest en route from the admissions unit to the operating theatre. At operation the liver was extensively injured, and the vena cava above and below the liver was torn. The patient failed to respond to continued cardiac massage and cross clamping of aorta and suprahepatic cava. The remaining six all died from haemorrhage; four had

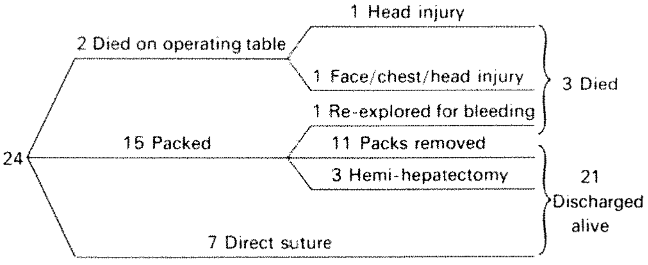

Figure 2 *Patients with Grade III trauma*

Table 6 *Computed tomographic scan grades with initial management*

CT grades*	Initial non-operative management ($n=12$)	Operative management/ operative grade ($n=6$)
1	Not reviewed	Not reviewed
2	2	0
3	8	3– 2–III 1–IV
4	2	3– 2–III 1–IV
5	0	0

* After Mirvis *et al.*[3]

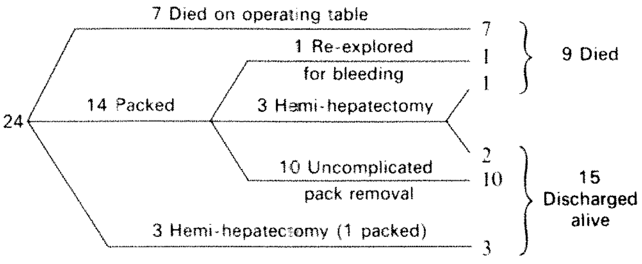
24
7 Died on operating table
7
1 Re-explored for bleeding
1
1
9 Died
14 Packed
3 Hemi-hepatectomy
2
10 Uncomplicated pack removal
10
3 Hemi-hepatectomy (1 packed)
3
15 Discharged alive

Figure 3 *Patients with Grade IV trauma*

Table 7 *Patients treated by packing*

Grade*	Number packed	Number packed and transferred	Deaths
III	15	11	1
IV	14	10	2

* After Calne *et al.*[2]

additional major chest injuries. Bleeding was uncontrollable in spite of packing or hemi-hepatectomy. The ninth death was the only fatality in a patient transferred to Addenbrooke's after primary packing. At the initial operation haemorrhage from the under surface of the right lobe was controlled by packing. At 24 h it was clear that the patient was actively bleeding and he was returned to theatre and re-explored. However, the bleeding could not be controlled and he died from exsanguination.

Fourteen patients with grade IV injuries were managed by packing; one further patient had a hemi-hepatectomy with placement of packs as part of the initial procedure. Three patients had a hemi-hepatectomy at the time of removal of the packs; two patients had a hemi-hepatectomy performed for bleeding which was not controlled by packing. Two patients subsequently developed subphrenic collections which were drained percutaneously, and five had pleural effusions requiring drainage.

Of the total of 29 patients treated by packing (*Table 7*), 21 were packed elsewhere and subsequently transferred to Cambridge; over half were supra-regional referrals, from as far afield as Dorset, North Yorkshire and Gwent. Three died, one on day 12 from associated injuries and two from continued bleeding requiring reoperation. A major head injury contributed to the death of one of these.

Patients initially managed non-operatively

Of the 18 patients who were examined by CT scanning, six were haemodynamically unstable and underwent immediate laparotomy. The remaining 12 patients with evidence of trauma on CT scanning (*Table 6*) were initially managed non-operatively. Three developed large intrahepatic collections which were drained at open surgery (on day 10 in two, and day 16 in the third). A fourth patient developed a large abscess communicating with an injured right kidney; this was successfully drained percutaneously. The remaining eight patients recovered without any operative procedure and did not develop significant collections meriting intervention of any sort.

Discussion

Previous experience in the management of hepatic trauma in this unit[2,4] has led to the evolution of a protocol for surgical intervention to secure control of haemorrhage from the injured liver. This intervention may involve direct suture, hepatic arterial ligation or resection; more often than not the judicious placement of perihepatic packs is sufficient to arrest haemorrhage. If packing adequately controls the haemorrhage the additional excessive blood loss which hepatic resection or hepatotomy and vascular ligation entails may be avoided. The primary blood loss can be replaced and haemodynamic status restored. Moreover, the risks of developing a coagulopathy are reduced and those clotting factors which have been consumed can be replaced. Should the patient subsequently require resection they are better prepared for it. This policy has enabled 21 patients with severe injuries to be packed as a first procedure and then transferred to us for pack removal and definitive surgery if required. All but one of these patients survived.

A second group of patients has emerged since the advent of CT scanning, namely that containing patients who are haemodynamically stable on admission or after initial resuscitation and who have isolated hepatic injury. This paper presents 12 such patients who were initially managed non-operatively. Three had persisting intrahepatic collections which were subsequently drained at open operation, and a fourth developed an intrahepatic abscess. The remaining eight patients made uneventful progress. All 12 patients recovered to be discharged with normal liver function.

Opinion about the optimum management of trauma is divided. The subject is complicated by the lack of a universally accepted classification, making comparison of reports difficult. In the absence of major trauma centres in this country, the admitting surgeon will probably be inexperienced in the management of hepatic trauma. If the patient's condition is stable and CT scanning is readily available, this is the investigation of choice. Resuscitation must precede scanning and the patient's condition should be stable, especially if the CT system has a long data acquisition time[3]. If CT scanning is not available and the clinical findings suggest blunt hepatic trauma, a diagnostic peritoneal lavage should be undertaken. However, while this may diagnose bleeding (and rupture of part of the gastrointestinal tract or pancreas), it cannot identify the source or amount of bleeding and may miss retroperitoneal haemorrhage. It is also invasive. CT scanning on the other hand can give an accurate idea about the amount and source of bleeding. The two investigations are best considered complementary rather than exclusive. Although important, the amount of haemoperitoneum does not predict failure of the non-operative approach[5]. More important indications for surgery on CT scanning are the extent of hepatic injury, with lacerations being more likely to require surgical intervention than intrahepatic haematoma, and the presence of any extrahepatic intra-abdominal injury. CT scanning is to be preferred to conventional ultrasonography, since its high resolution defines anatomy more clearly and administration of contrast allows better assessment of other visceral, especially renal, injuries. Furthermore, the new generation CT systems have short data acquisition times.

In children a policy of non-operative management for splenic trauma has long been advocated and successfully practised, and this policy has been extended to hepatic trauma[6,7]. A similar policy for isolated hepatic injuries in adults has been slower to evolve, but there are now several reports attesting to its success in selected cases[3,8,9–11].

When surgery is undertaken it is common to see no active bleeding from the hepatic wound; in such cases haematoma is evacuated but the clot left undisturbed. Bleeding from lacerations may be arrested by simple suture, although in our experience the areas sutured have often become necrotic at the time of second laparotomy 48 h later. More severe arterial bleeding is managed by selective hepatic artery ligation[12]. If temporary occlusion of the hepatic artery controls bleeding then that vessel or the lobar artery may be ligated. There is, however, a risk of hepatic necrosis, and in many cases accessory hepatic arteries arising from the left gastric artery or superior mesenteric artery are present and contribute to the bleeding. Such an approach will not arrest haemorrhage from injuries to portal and hepatic veins[13]. Continued bleeding is best treated by the placement of packs around the liver to tamponade any venous bleeding. Indeed, placement of packs early in the course of the laparotomy usually staunches haemorrhage and allows the anaesthetist to give adequate fluid replacement, platelets and fresh frozen plasma. If this succeeds in arresting haemorrhage then it is appropriate to close the abdomen and elect to re-explore the patient 48 h later. This period of time allows the patient to be stabilized and any coagulopathy to be corrected[14]; other injuries can also be stabilized. The 48 h interval represents the best compromise between stabilizing and avoiding pack-related sepsis. If the placement of packs and selective arterial ligation fail, then a major hepatic resection is the only procedure likely to save the patient's life.

Resections are of two types, resectional debridement or anatomical resection[15]. Resectional debridement involves extending the plane of injury to remove the involved parenchyma, and usually entails removal of at least one hepatic segment. Anatomical lobectomy is performed along anatomical planes. It is generally a larger procedure, and its popularity as the procedure of choice is decreasing due to associated high mortality[16], and the role of abdominal packing is being re-evaluated.

The opponents of packing cite a high incidence of intra-abdominal infection and low success[17,18]; however, this only occurs frequently when packing is used as a last resort. The authors' experience and that of others has been that an early decision to pack allows stabilization of the patient, and it is particularly useful in the face of an evolving coagulopathy[1,19,20]. Broad spectrum antibiotics should be given while the packs are *in situ*, and the packs should be removed once the patient is stable and the coagulopathy corrected. This takes about 48 h. Early reoperation and repacking or resection is appropriate if bleeding continues, although Fandrich *et al.*[21] have reported successful angiographic embolization of the hepatic artery under these circumstances.

Recently, surgeons in Hannover have performed two-stage procedures for patients with extreme trauma involving total hepatectomy with portocaval anastomoses, followed by liver transplantation when a new liver becomes available. This technique was originally performed to rescue patients with acute liver or graft failure[22]. Ringe *et al.*[23] have now performed two such transplants for trauma with good results.

The successful management of severe liver trauma also demands intensive anaesthetic and postoperative care. Patients require aggressive resuscitation, including early administration of platelets and coagulation factors. The patients may become acidotic and profoundly hypothermic, features which contribute to coagulopathy[24]. The availability of an autotransfusion cell saver allows rapid infusion of blood and the avoidance of hypothermia, as well as reducing the demands on the blood bank. The requirement for massive transfusion and the high incidence of associated chest injuries also place these patients at risk of the acute lung injury syndrome (shock lung). All blood products must be filtered from the outset and administration of crystalloid solutions minimized; careful monitoring after operation is necessary to avoid fluid overload, and haemofiltration may be necessary to off-load excess water.

In conclusion, we recommend the following management protocol.

1. Assessment – CT scanning and peritoneal lavage

On admission, the patient should be assessed and resuscitated as appropriate. If they remain unstable, emergency laparotomy is indicated. The stable patient should have an immediate CT scan if available. A peritoneal lavage should be performed if CT scanning is not readily available (or to provide additional information). If there is clinical or radiological evidence of continued bleeding, or injury to other intra-abdominal organs, laparotomy is indicated; if not, close monitoring and an expectant non-operative policy may be followed. However, in patients with major head or spinal injuries, where clinical signs may be misleading or absent, early exploratory laparotomy (or diagnostic laparoscopy) may be appropriate.

2. Laparotomy – packing

If laparotomy is indicated because of bleeding, the surgery should be as conservative as possible. Frequently bleeding will have stopped, in which case the clot should not be disturbed; active bleeding is dealt with by suture and ligation. Continued bleeding from deep lacerations is dealt with by the placement of large rolls of gauze above and around the liver.

3. Laparotomy – hepatic artery ligation and resection

Bleeding not controlled by suture/ligation or packing requires more extensive surgery. Selective hepatic artery ligation should be performed, if temporary occlusion is beneficial. If this is unsuccessful then major resection or debridement is indicated.

4. Hepatectomy and transplantation

In extreme cases total hepatectomy with portocaval anastomosis may be life-saving, followed by emergency liver transplantation.

Faced with major hepatic trauma the surgeon should not feel obliged to embark on heroic unpracticed operative procedures. We have shown that non-operative management, conservative surgery where indicated, and judicious perihepatic packing and transfer to a specialized centre, are safe and effective for many of these life-threatening injuries.

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References

1. Feliciano DV, Mattox KL, Burch JM, Bitondo CG, Jordan GL. Packing for control of hepatic haemorrhage. *J Trauma* 1986; **26**: 738–43.
2. Calne RY, Wells FC, Forty J. Twenty-six cases of liver trauma. *Br J Surg* 1982; **69**: 365–8.
3. Mirvis SE, Whitley NO, Vainwright JR, Gens DR. Blunt hepatic trauma in adults: CT-based classification and correlation with prognosis and treatment. *Radiology* 1989; **171**: 27–32.
4. Calne RY, McMaster P, Pentlow BD. The treatment of major liver trauma by primary packing with transfer of the patient for definitive treatment. *Br J Surg* 1979; **66**: 338–9.
5. Federico JA, Horner WR, Clarke DE, Isler RJ. Blunt hepatic trauma. Non-operative management in adults. *Arch Surg* 1990; **125**: 905–9.
6. Trauma Committee, Canadian Association of Paediatric Surgeons. Canadian Association of Paediatric Surgeons: Liver trauma study. *J Pediatr Surg* 1989; **24**: 1035–40.
7. Oldham KT, Guice KS, Ryckman F, Kaufman RA, Martin LW, Noseworthy J. Blunt liver injury in childhood: evolution of therapy and current perspective. *Surgery* 1986; **100**: 542–9.
8. Moon KL, Federle MP. Computed tomography in hepatic trauma. *AJR* 1983; **141**: 309–14.
9. Meyer AA, Crass RA, Lim RC, Jeffrey RB, Federle MP, Trunkey DD. Selective non-operative management of blunt liver injury using computed tomography. *Arch Surg* 1985; **120**: 550–4.
10. Farnell MB, Spencer MP, Thompson E, Williams HJ, Mucha P, Ilstrup DM. Non-operative management of blunt hepatic trauma in adults. *Surgery* 1988; **104**: 748–56.
11. Hiatt JR, Harrier HD, Koenig BV, Ransom KJ. Nonoperative management of major blunt liver injury with haemoperitoneum. *Arch Surg* 1990; **125**: 101–3.
12. Mays ET, Conti S, Fallahzadeh H, Rosenblatt M. Hepatic artery ligation. *Surgery* 1979; **86**: 536–41.
13. Flint LM, Polk HC. Selective hepatic artery ligation: limitations and failures. *J Trauma* 1979; **19**: 319–23.
14. Saifi J, Fortune JB, Graca L, Shah DM. Benefits of intra-abdominal pack placement for the management of nonmechanical haemorrhage. *Arch Surg* 1990; **125**: 119–22.
15. Hollands MJ, Little JM. The role of hepatic resection in the management of blunt liver trauma. *World J Surg* 1990; **14**: 478–82.
16. Moore FA, Moore EE, Seagraves A. Non-resectional management of major hepatic trauma. *Am J Surg* 1985; **150**: 725.
17. Ivatury RR, Nallathambi M, Gunduz Y, Constable R, Rohman M, Stahl WM. Liver packing for uncontrolled haemorrhage: a reappraisal. *J Trauma* 1986; **26**: 744–51.
18. Bender JS, Geller ER, Wilson RF. Intra-abdominal sepsis following liver trauma. *J Trauma* 1989; **29**: 1140–4.
19. Svoboda JA, Peter ET, Dang CV, Parks SN, Ellyson JH. Severe liver trauma in the face of coagulopathy. A case for temporary packing and early reoperation. *Am J Surg* 1982; **144**: 717–21.
20. Carmona RH, Peck DZ, Lim RC Jr. The role of packing and planned reoperation in severe hepatic trauma. *J Trauma* 1984; **24**: 779–82.

21. Fandrich BL, Gnanadev DA, Jaecks R, Boyle W. Selective hepatic artery embolization as an adjunct to liver packing in severe hepatic trauma: case report. *J Trauma* 1989; **29**: 1716–18.
22. Ringe B, Pichlmayr R, Lübbe N, Bornscheuer A, Kuse E. Total hepatectomy as temporary approach to acute hepatic or primary graft failure. *Transplant Proc* 1988; **20**: 552–7.
23. Ringe B, Pichlmayr R, Ziegler H *et al.* Management of severe hepatic trauma by two stage total hepatectomy and subsequent liver transplantation. *Surgery* 1991; **109**: 792–5.
24. Elerding SC, Aragon GE, Moore EE. Fatal hepatic haemorrhage after trauma. *Surgery* 1979; **138**: 883–8.

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Case report

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Intestinal plication: an alternative to tapered jejunostomy in functional small bowel obstruction

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Small bowel dilatation is a feature of adaptation which follows extensive small bowel resection; it may result in functional obstruction. A similar type of dilatation and obstruction has been reported in children with small bowel atresia and intestinal plication has been found to be an effective form of management. We report a case in which intestinal plication was successfully used to deal with functional intestinal obstruction complicating short gut syndrome.

Case report

A 25-day-old full-term female infant was admitted with peritonitis. Following resuscitation, laparotomy disclosed infarction of the distal 85 per cent of the small bowel. A large volume of infected intraperitoneal chylous fluid was present and a multiloculated mesenteric chylous cyst occupied the mesentery of the remaining viable jejunum. The cause of the infarction was unclear. Gangrenous intestine was resected; 45 cm of normal proximal jejunum and 5 cm of doubtfully viable terminal ileum remained and both bowel ends were separately exteriorized.

Subsequent attempts at oral feeding resulted in high output stomal dysfunction and resultant dehydration. Various attempts at dietary manipulation were unsuccessful, requiring continued intravenous nutrition. Small bowel barium studies were performed 3 months after operation and showed gross jejunal distension with poor peristaltic activity. No obstructing lesion was seen. Bacterial colonization of the small bowel was documented.

At repeat laparotomy 6 months after the first operation the remaining bowel was massively dilated. The multiloculated mesenteric cyst remained unchanged. Intestinal plication (*Figure 1*), as described by de Lorimier and Harrison[1], was performed and intestinal continuity was restored with a Bishop–Koop anastomosis (*Figure 2*).

Oral feeding was gradually reintroduced and parenteral nutrition discontinued a few weeks after the second operation. The stoma was closed and the child was discharged from hospital at 9 months of age.

The patient is now 4 years old and is on the 50th centile for height and weight, tolerates a normal diet and has no steatorrhoea.

Discussion

Dilatation of the small bowel is an integral aspect of adaptation[2]. The resulting increase in absorptive surface area of the intestine will be beneficial to the patient but sometimes the compromised intestinal transit may be disadvantageous[3]. In the patient described above, this resulted in luminal bacterial overgrowth and functional obstruction.

Surgical intervention in such cases is required to deal with the problem of ineffective peristaltic activity. Procedures used in the past include vagotomy and pyloroplasty, reversed small bowel segments, recirculating small bowel loops, colon interposition and 'neo-ileocaecal valves'[4], but the results have been unpredictable. Intestinal loop lengthening[5], although an attractive concept, is a difficult operation and has the additional disadvantage of requiring complex suture or staple lines.

Reduction in luminal diameter with subsequent improvement in peristaltic activity is effectively achieved by tapered jejunostomy[6], but this can also be produced using the technique of small bowel plication which has been described for the treatment of small bowel dilatation found in atresia[1]. We have

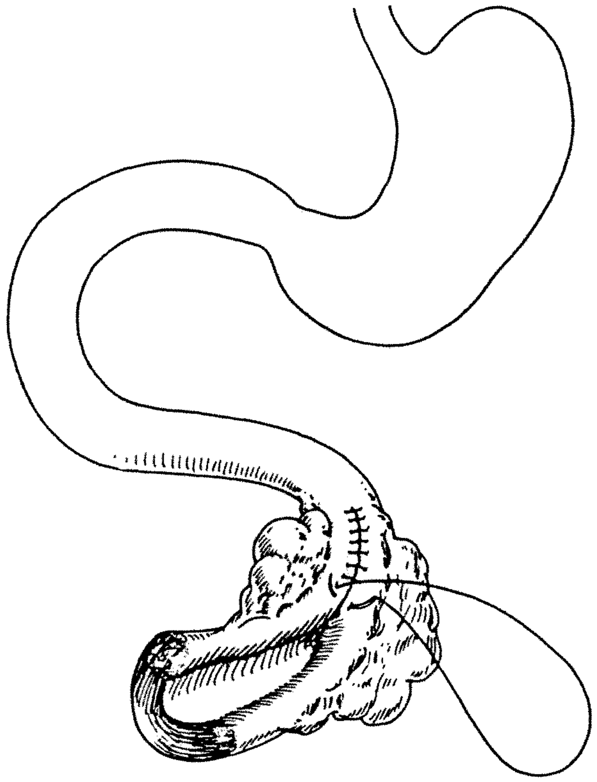

Figure 1 *The dilated distal jejunum was plicated by invaginating with the index finger. The new antemesenteric border was fashioned using a continuous suture*

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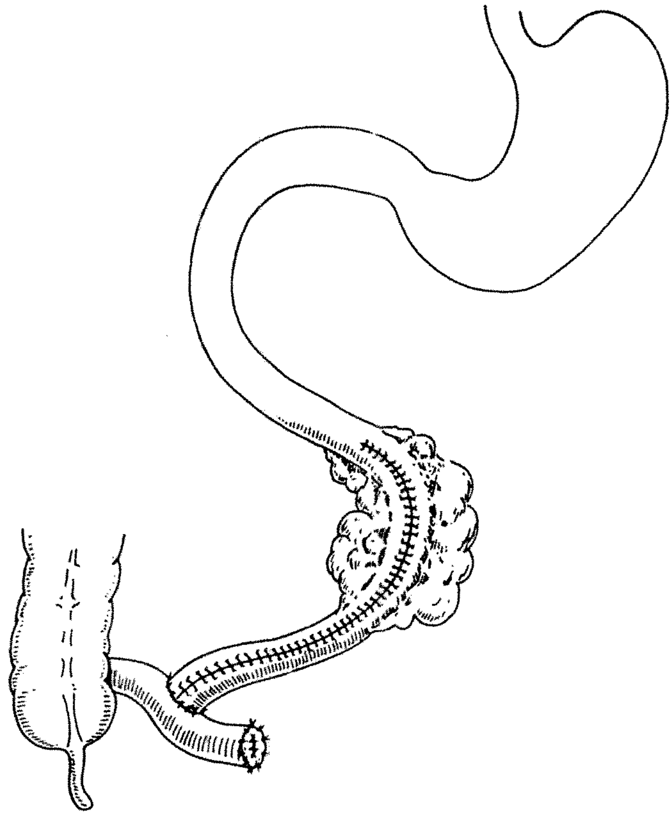

Figure 2 *The plicated jejunum was anastomosed end-to-side to the remaining terminal ileum, the end of which was exteriorized*

previously used this technique successfully in two cases of functional obstruction complicating small bowel atresia. The attractions of this method are avoidance of a long anastomotic suture line and preservation of the entire surface of the bowel which is an important consideration in patients with short bowel syndrome. The success of a relatively simple surgical technique in this patient encourages us to endorse its more widespread use in patients with functional obstruction due to short gut syndrome.

References

1. de Lorimier AA, Harrison MR. Intestinal plication in the treatment of atresia. *J Pediatr Surg* 1983; **18**: 734–7.
2. Wilmore DW, Dudrick SJ, Daly JM, Vars HM. The role of nutrition in the adaptation of the small bowel intestine after massive resection. *Surg Gynecol Obstet* 1971; **132**: 673–80.
3. de Lorimier AA, Normal DA, Gooding CA, Preger L. A model for the cinefluoroscopic and manometric study of chronic intestinal obstruction. *J Pediatr Surg* 1973; **8**: 785–91.
4. Schwartz MX, Maeda K. Short bowel syndrome in infants and children. *Pediatr Clin North Am* 1985; **32**: 1265–79.
5. Bianchi A. Intestinal loop lengthening – a technique for increasing small intestinal length. *J Pediatr Surg* 1980; **15**: 145–51.
6. Thomas CG, Carter JM. Small intestinal atresia. The critical role of a functioning anastomosis. *Ann Surg* 1974; **179**: 663–70.

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Graft *versus* host disease in small bowel transplantation

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Quantities of organized lymphoid tissue in small bowel allografts may cause graft versus *host disease (GVHD) following transplantation. This study examines the effect of graft mesenteric lymphadenectomy on development of GVHD following small bowel transplantation in rats. GVH reactivity was assessed by measuring the degree of graft cell emigration to the host. In the PVG to DA strain combination, graft mesenteric lymphadenectomy led to a significant reduction in graft cell colonization of host lymphoid tissues from 40–50 per cent to 25–35 per cent. Transplantation from PVG to (PVG × DA)F1 hybrids caused fatal GVHD within 21 days whereas when DA donors were used survival was over 30 days. When mesenteric lymphadenectomy was performed on PVG donors, host survival increased by only 3–4 days. Mesenteric lymphadenectomy in DA donors led to long-term recipient survival with no GVHD. Intensity of GVHD following rat small bowel transplantation is a strain-dependent phenomenon and graft mesenteric lymphadenectomy does not always prevent GVHD. The mucosa may have an important immunological role.*

Graft *versus* host disease (GVHD) is an immunological phenomenon best seen following allogeneic bone marrow grafting[1]. It may follow experimental or clinical small bowel transplantation[2–6] or multiple organ transplants in which the spleen is included in the graft[7]. The grafted tissue 'recognizes' foreign host antigens and mounts an immunological reaction[8] through immunocompetent T lymphocytes within the graft[9,10]. The balance between GVHD and rejection is dynamic and allogeneic transplantation rejection and GVHD may develop at different times. Dominant rejection processes destroy graft cells and preclude an overt GVH response.

Small bowel transplantation has had limited success in recent clinical practice[6,11]. GVHD is a significant problem following small bowel transplantation and is attributed to the large amount of organized lymphoid tissue included in the graft (mesenteric lymph nodes, Peyer's patches and lamina propria lymphocytes). The small bowel mucosa contains approximately 10^6 lymphoid cells per gram of tissue[12]. Experimental and clinical evidence suggests that GVHD is not prevented using standard immunosuppressive regimens in bone marrow transplantation[13] or small bowel transplantation[3,6].

A large proportion of the lymphoid tissue in small bowel grafts is included in the mesenteric lymph nodes. Measures to deplete T lymphocyte numbers selectively in the mesenteric lymph nodes might reduce GVHD without leading to mucosal damage. The mucosa would be at risk in manoeuvres designed to deplete T lymphocytes in Peyer's patches and the lamina propria.

This study assesses the effect of graft mesenteric lymphadenectomy on the development of GVH responses following experimental small bowel transplantation in the rat.

Materials and methods

Surgery

Heterotopic vascularized accessory small bowel transplantation was carried out in rats using standard microvascular techniques[2] in which the two ends of the transplanted bowel were exteriorized as stomas in the form of a Thiry-Vella fistula.

Mesenteric lymphadenectomy

In experimental groups the mesenteric lymph nodes were removed before harvesting the graft. These nodes in the rat lie in a discrete strip running parallel to the superior mesenteric artery and complete removal is easily achieved. The weight of tissue removed was similar in the two strains of rat used.

Assessment of GVH reactivity

Fully allogeneic small bowel transplantation was carried out between two inbred strains of rat (PVG and DA) which differed at the major histocompatibility complex (MHC). All recipients were given cyclosporin 15 mg/kg per day by intramuscular injection from the day of transplantation, a regimen which has been shown to prevent acute rejection[10]. Seven days after transplantation the lymphoid tissues of the host were harvested, snap-frozen and stored at −70°C before analysis.

The host lymphoid tissues (spleen, mesenteric nodes and Peyer's patches) were sectioned and subjected to immunohistochemical analysis using an indirect immunoperoxidase technique. Two mutually exclusive monoclonal antibodies were used; MN4 which specifically recognizes DA rat Class I MHC antigens and OX27 which recognizes PVG Class I MHC antigens[14,15]. After staining, the number of positive (graft derived) cells was counted and expressed as a percentage of all the cells in the tissues. The areas selected for study were those which emigrating cells preferentially colonize: thymus-dependent areas of the spleen, mesenteric nodes and Peyer's patches[16].

Experimental groups used to assess GVH reactivity

Groups of rats were transplanted as follows: DA to PVG, PVG to DA, and PVG to DA with mesenteric lymphadenectomy. Six animals were included in each group.

Assessment of GVHD

A specific model of GVHD without concomitant rejection can be achieved by using inbred parental donors and F1 hybrid recipients[2]. If transplantation is carried out from parental strain (A) to F1 hybrid offspring strain (A × B)F1 then the host (A × B)F1 recognizes graft antigens (A) as self and no rejection ensues. In contrast, the graft (A) recognizes host antigens (A × B) as foreign and mounts an immunological reaction against the host. These models are of value in analysing details of immunological reactions between graft and host. In the rat, small bowel transplantation from parent to F1 hybrids usually leads to death from GVHD in 2–3 weeks[2,4].

Experimental groups in this study included (A) PVG to (PVG × DA)F1 (controls); (B) PVG with graft mesenteric lymphadenectomy to (PVG × DA)F1; (C) DA to (PVG × DA)F1 (controls); (D) DA with mesenteric lymphadenectomy to (PVG × DA)F1. Following transplantation signs of development of GVHD were observed; cutaneous erythema, hunched posture and progressive weight loss. Survival was recorded in each group. Autopsy was carried out in all cases. Histological evidence of GVHD was sought by post-mortem

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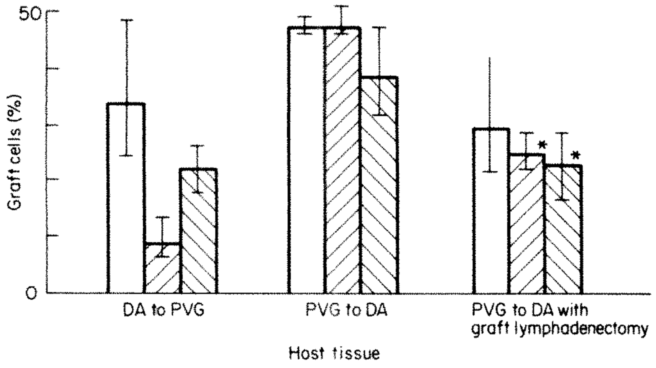

Figure 1 *Fully allogeneic small bowel transplantation: graft cell emigration to host lymphoid tissues after 7 days of immunosuppression by cyclosporin.* □, *Spleen;* ▨, *mesenteric node;* ▧, *Peyer's patch. Values are median (range) for each group. Statistical comparison using Wilcoxon rank sum test.* * $P < 0\cdot05$ *compared with transplantation without graft lymphadenectomy (PVG to DA)*

assessment and histological examination of host lymphoid tissues and liver.

Results

Effect of strain combination and mesenteric lymphadenectomy on GVH reactivity

The degree of cell migration from graft to host differed according to whether transplantation was carried out from PVG donors to DA recipients, or from DA donors to PVG recipients (*Figure 1*). Transplantation from PVG to DA was associated with a greater degree of cellular migration, suggesting a stronger degree of GVH reactivity from PVG towards DA antigens.

The stronger strain combination for GVH reactivity (PVG to DA) was subsequently used to test the effect of mesenteric lymphadenectomy. Seven days after small bowel transplantation from PVG to DA rats the T cell areas of the host spleen, mesenteric lymph nodes and Peyer's patches contained 40–50 per cent of cells which were of graft origin. After transplantation from DA to PVG, at the same time point, only 10–30 per cent of the cells in the host lymphoid tissues had come from the graft. Graft mesenteric lymphadenectomy significantly reduced the cellular emigration from graft to host in the PVG strain combination to 30–35 per cent.

Effect of strain combination and mesenteric lymphadenectomy on GVHD disease

In the DA to (PVG × DA)F1 combination, survival after small bowel transplantation was significantly longer than in the PVG to (PVG × DA)F1 combination. Although all the rats in group C (DA to (PVG × DA)F1) developed symptoms of GVHD, a degree of recovery occurred in two, and one survived to >150 days. Group A (PVG to (PVG × DA)F1) all developed severe GVHD leading to death by 21 days. In the weaker (DA to (PVG × DA)F1) strain combination graft mesenteric lymphadenectomy (group D) led to long-term survival in all rats, with no evidence of GVHD (*Figure 2*). In group B graft mesenteric lymphadenectomy delayed fatal GVHD by only 3–4 days.

At post-mortem examination the clinical evidence of GVHD in groups A, B and C was confirmed by finding decreased intra-abdominal adiposity, relative splenomegaly, enlarged lymph nodes and thinning and distension of host ileum. Histological examination of host lymphoid tissues showed a loss of architecture and the liver showed a periportal infiltrate: findings typical of GVHD[17,18]. In group D (DA with mesenteric lymphadenectomy to (PVG × DA)F1) no macroscopic or microscopic stigmata of GVHD were found when rats were killed at 150 days.

Discussion

Cellular migration from graft into host tissues is a measure of GVH reactivity following small bowel transplantation[16], when there is an early and progressive infiltration of graft tissues by host leucocytes whether or not acute rejection takes place[19]. MHC antigens on the host cells are recognized as foreign by the large number of graft lymphocytes and the graft mounts an immune response against the host. Graft lymphocytes proliferate and emigrate into the host where they can be identified in lymphoid tissues[16] and in peripheral blood[6].

There is a significant difference in the intensity of this GVH reactivity in the two strain combinations tested. In the combination in which there is an aggressive GVH response (PVG to DA) transplantation of the small bowel without the associated mesenteric lymph nodes still produces a substantial GVH response. Following semi-allogeneic transplantation, graft mesenteric lymphadenectomy does not necessarily prevent GVHD and recipient death with a wide spectrum of activity ranging from mild transient GVHD (despite an intact graft) to fatal GVHD (following graft mesenteric lymphadenectomy). The effect appears to be a strain-dependent phenomenon. Prevention of GVHD by graft mesenteric lymphadenectomy has previously been demonstrated in other rat strain combinations[20,21]. No previous study has shown that small bowel transplantation following graft mesenteric lymphadenectomy can lead to fatal GVHD. It has been suggested that clinical transplantation efforts to prevent GVHD need be directed only at the mesenteric nodes. This new finding shows that the protective effect of mesenteric lymphadenectomy is a strain-dependent phenomenon and other aspects need further study.

The differing responses might be explained by differing distribution of lymphocytes between the mesenteric nodes, Peyer's patches and lamina propria in the two different strains. There is no evidence for this and histological examination of these tissues revealed no obvious differences in cellular composition between the two rat strains. It is more likely that the difference is the result of varying intensity of immunological responsiveness in different strain combinations. A greater intensity of cellular migration from PVG grafts to DA hosts than from DA grafts to PVG hosts supports this view.

It might be expected that graft mesenteric lymph nodes would mount a stronger GVH response than the mucosa because of their size and because normal lymphocyte traffic is from lamina propria to Peyer's patches and to lymph nodes. Cell preparations from mesenteric lymph nodes incude a fatal GVH response if injected intraperitoneally in a semi-allogeneic model[22]. *In vitro* systems demonstrate that mucosal lymphocytes can mount a GVH response[23] although intraepithelial lymphocytes probably cannot[24].

Various experimental means have been used in small bowel

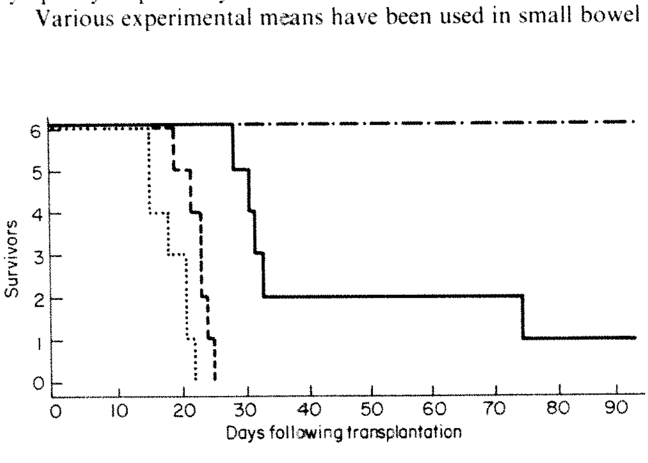

Figure 2 *Life table demonstrating mortality caused by GVHD in different strain combinations with and without graft mesenteric lymphadenectomy.* ·····, *PVG to PVG × DA;* ——, *PVG to PVG × DA with lymphadenectomy;* -----, *DA to PVG × DA;* – · – · –, *DA to PVG × DA with lymphadenectomy*

transplantation to prevent GVHD. Immunosuppression with cyclosporin is not uniformly successful[3,10]. Donor[2] or graft[20,25] irradiation or donor pretreatment with anti-lymphocyte serum[26] is more successful. Donor pretreatment needs to commence at least 2 days before transplantation and would not be a practical clinical option. Graft irradiation is a possible alternative, but it may cause T lymphocyte destruction and radiation damage to the mucosa may occur. Mucosal shielding could be used but the results of the current study suggest that this would not guarantee protection from GVHD.

Graft mesenteric lymphadenectomy would not be practicable in human small bowel transplantation because of the anatomical arrangement of the mesenteric nodes. Graft perfusion with a specific T lymphocyte toxin might prevent GVHD and in bone marrow transplantation such a toxin (a combination of an anti-T lymphocyte monoclonal antibody with ricin A-chain) is effective[27].

Future efforts to prevent GVHD following experimental and clinical small bowel transplantation should be directed at T lymphocytes in the graft lamina propria and Peyer's patches as well as those in the mesenteric lymph nodes. In experimental models of small bowel transplantation the intensity of GVH reactivity depends on the strain combination used.

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References

1. Slavin RE, Santos GW. The graft *versus* host reaction in man after bone marrow transplantation: pathology, pathogenesis, clinical features and implications. *Clin Immunol Immunopathol* 1973; **1**: 472–98.
2. Monchik GJ, Russell PS. Transplantation of small bowel in the rat: technical and immunological considerations. *Surgery* 1971; **70**: 693–702.
3. Diflo T, Maki T, Balogh K, Monaco AP. Graft *versus* host disease in fully allogeneic small bowel transplantation in the rat. *Transplantation* 1989; **47**: 7–11.
4. Kirkham RL. Small bowel transplantation. *Transplantation* 1984; **37**: 429–33.
5. Cohen Z, Silverman RE, Wassef R, Levy GA, Burnstein M, Cullen J *et al.* Small intestinal transplantation using cyclosporine. *Transplantation* 1986; **42**: 613–21.
6. Grant D, Wall W, Mimeault R, Zhong R, Ghent C, Garcia B *et al.* Successful small bowel/liver transplantation. *Lancet* 1990; **i**: 181–4.
7. Starzl TE, Iwatsuki S, Shaw BW Jr, Greene DA, Van Thiel DH, Nalesnik MA *et al.* Pancreaticoduodenal transplantation in humans. *Surg Gynecol Obstet* 1984; **159**: 265–72.
8. Simonsen M. Graft *versus* host reactions. Their natural history and applicability as tools of research. *Progr Allergy* 1962; **6**: 349–467.
9. Mason DW, Pugh CW, Webb M. The rat mixed lymphocyte culture: roles of a dendritic cell in intestinal lymph and T cell subsets defined by monoclonal antibodies. *Immunology* 1981; **44**: 75–87.
10. Kirkman RL, Lear PA, Madara JL, Tilney NL. Small intestine transplantation in the rat – immunology and function. *Surgery* 1984; **96**: 280–6.
11. Schroeder P, Goulet O, Lear PA. Small bowel transplantation: the European experience. *Lancet* 1990; **ii**: 110–11.
12. Goodacre R, Davidson R, Singal D, Bienstock J. Morphology and functional characteristics of human intestinal lymphoid cells isolated by a mechanical technique. *Gastroenterology* 1979; **76**: 300–8.
13. Deeg HJ, Loughran TP Jr, Storb R, Kennedy MS, Sullivan AM, Doney K *et al.* Treatment of human acute graft *versus* host disease with antithymocyte globulin and cyclosporine ±methylprednisolone. *Transplantation* 1985; **40**: 162–6.
14. Milton AD, Fabre JW. Massive induction of donor-type class I and class II MHC antigens in rejecting cardiac allografts in the rat. *J Exp Med* 1985; **161**: 98–112.
15. Jefferies WA, Green JR, Williams AF. Authentic T helper CD4 (W3/25) antigen on rat peritoneal macrophages. *J Exp Med* 1985; **162**: 117–27.
16. Lear PA, Cunningham AJ, Crane PW, Wood RFM. Patterns of lymphocyte migration in small bowel transplants. *Transplant Proc* 1989; **21**: 2881–2.
17. Grant D, Zhong R, Gunn H, Duff J, Garcia B, Keown P *et al.* Graft *versus* host disease associated with intestinal transplantation in the rat. *Transplantation* 1989; **48**: 545–9.
18. Schraut WH, Lee KKW, Dawson PJ, Hurst RD. Graft *versus* host disease induced by small bowel allografts. *Transplantation* 1986; **41**: 286–90.
19. Ingham Clark CL, Cunningham AJ, Crane PW, Wood RFM, Lear PA. Lymphocyte infiltration patterns in rat small bowel transplants. *Transplant Proc* 1990; **22**: 2460.
20. Deltz E, Ulrichs K, Schack T, Friedrichs B, Muller-Ruchholtz W, Muller-Hermelink H-K *et al.* Graft-*versus*-host reaction in small bowel transplantation and possibilities for its circumvention. *Am J Surg* 1986; **151**: 379–86.
21. Luck R, Klempnauer J, Steiniger B. Transplantation of MHC incompatible vascularised mesenteric lymph nodes: identical pattern of lethal graft-*vs*-host disease as induced by small bowel grafts. *Transplant Proc* 1990; **22**: 2332.
22. Pirenne J, Lardinois F, D'Silva M, Fridman V, Boniver J, Mahieu P. Relevance of mesenteric lymph nodes to graft-*versus*-host disease following small bowel transplantation. *Transplantation* 1990; **50**: 711–14.
23. MacDonald TT, Philip BC. Mouse Peyer's patches contain T cells capable of inducing the graft *versus* host reaction. *Transplantation* 1978; **26**: 162–5.
24. Baca M, Mowat AMcI, Mackenzie S, Parrott DMV. Functional characteristics of intra-epithelial lymphocytes from mouse small intestine. III. Inability of IEL to induce a systemic graft *versus* host reaction is because of failure to migrate *in vivo*. *Gut* 1987; **28**: 1267–74.
25. Lee KKW, Schraut WH. *In vitro* allograft irradiation prevents graft *versus* host disease in small bowel transplantation. *J Surg Res* 1985; **38**: 364–72.
26. Shaffer D, Maki T, Demichele SJ, Karlstad MD, Bistrian BR, Balogh K *et al.* Prevention of graft *versus* host disease with preservation of allograft function by donor pretreatment with antilymphocyte serum. *Transplantation* 1988; **45**: 262–9.
27. Filipovich AH, Vallera DA, Youle RJ, Haake R, Blazar BR, Arthur D *et al.* Graft *versus* host disease prevention in allogeneic bone marrow transplantation from histocompatible siblings. A pilot study using immunotoxins for T cell depletion of donor bone marrow. *Transplantation* 1987; **44**: 62–9.

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c-*myc* protein product is a marker of DNA synthesis but not of malignancy in human gastrointestinal tissues and tumours

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*c-*myc *is a conserved cellular gene. The gene product is a nuclear-bound 62 000 molecular weight phosphoprotein (p62c-*myc*). Although p62c-*myc *levels have been measured in colorectal cancers, little is known about the expression of the protein in upper gastrointestinal tumours and tissues. Studies were performed on tumour and mucosal specimens from 87 patients with colorectal cancer, from two with polyposis coli, from six with squamous oesophageal carcinomas and from 18 with gastric carcinomas. The mean p62c-*myc *content was measured in units of fluorescence in the G1 diploid and G2 diploid peaks of the cell cycle by multiparameter flow cytometry using the 6E10 antibody. The nuclear p62c-*myc *content increased with DNA synthesis in tumours and mucosa. G2 levels of p62c-*myc *were higher in glandular mucosa than in adenocarcinomas. No differences in peak nuclear c-*myc *expression were found in relation to histological grade or to anatomical site of colorectal tumours. There was a broadly inverse relationship between G2 p62c-*myc *levels in tumours and mucosa and their* in vivo *5-bromo-2′-deoxyuridine labelling indices. Nuclear p62c-*myc *levels are cell cycle related but the protein has not been shown to be a marker of increased tissue proliferation or of gastrointestinal malignancy. The reduction of the nuclear p62c-*myc *content of many adenocarcinoma cells compared with glandular mucosa cells suggests that reduced synthesis or nuclear retention of the normal protein may be a factor in the development of gastrointestinal adenocarcinomas, although the mechanism by which this may occur is not clear.*

c-*myc* is a cellular gene, sited on chromosome 8 at location q24 (Reference 1). It shows differential expression between resting and proliferating cells and is highly conserved between species[2–4]. Its gene product is a 439-amino acid, 62 000 molecular weight phosphoprotein (p62c-*myc*) whose structure and function have been described[5–8]. Little is known about its expression in upper gastrointestinal tissues and tumours. The protein can be detected in fresh, ethanol, methanol or formalin fixed specimens using monoclonal antibodies such as 6E10, by multiparameter flow cytometry (MFCM), by Western blotting and by histochemistry. The type of fixative and analysis may have an important bearing on the results obtained.

There is contradictory evidence about whether the c-*myc* gene is overexpressed in colorectal cancer. Moreover, the selective expression of a gene such as c-*myc* in the cell cycle does not necessarily indicate that it has a regulatory role[9]. Deregulation and overexpression of c-*myc* may be associated with loss of allelic markers on chromosome 5q, which is also known to contain the gene 'apc' associated with familial adenomatous polyposis[10,11]. Dolcetti *et al.*[12] found by DNA hybridization that only one of 44 colorectal tumours showed overexpression of c-*myc*. Watson[13] measured the nuclear content of p62c-*myc* in colonic polyps and tumours by MFCM and found that p62c-*myc* is less well expressed in poorly differentiated colorectal tumours. This finding correlated with c-*myc* mRNA transcript levels measured by Northern blotting[14]. p62c-*myc* may have a role in the evolution of colonic neoplasia and be a prognostic indicator for colonic tumours[15,16]. Finley *et al.*[17] found that c-*myc* mRNA but not N-*myc* or L-*myc* mRNA was significantly overexpressed in colorectal adenomas and tumours compared with normal mucosa. Constantini *et al.*[18] found a wide variation in c-*myc* mRNA expression within tumours and adenomas by *in situ* hybridization.

c-*myc* is expressed in archival (formalin fixed) specimens of colorectal mucosa, but at significantly higher levels in colorectal carcinomas[19]. In both mucosa and tumour cell nuclei the level of p62c-*myc* increases through the cell cycle. The p62c-*myc* in tumour cells, unlike deep crypt mucosa, may be both nuclear and cytoplasmic in distribution[20]. The p62c-*myc* may be expressed throughout the thickness of the normal human colon epithelium and not preferentially in any one compartment[21].

To test the hypothesis that nuclear-bound p62c-*myc* may be a marker of neoplasia in the gastrointestinal tract, we have compared the expression of the nuclear protein in both tumours and mucosa by MFCM. We have also measured its cell cycle related expression in ethanol fixed material, in which the proliferation kinetics as measured by 5-bromo-2′-deoxyuridine (BrdUrd) incorporation were known.

Patients and methods

This study was performed on biopsies of colorectal, gastric and oesophageal carcinomas and tissues excised during surgery which were labelled with BrdUrd. The method of analysis to obtain an *in vivo* BrdUrd labelling index and potential doubling time (T_{pot}) by MFCM analysis has recently been reported[22].

At the time of surgery, biopsies were immediately excised from

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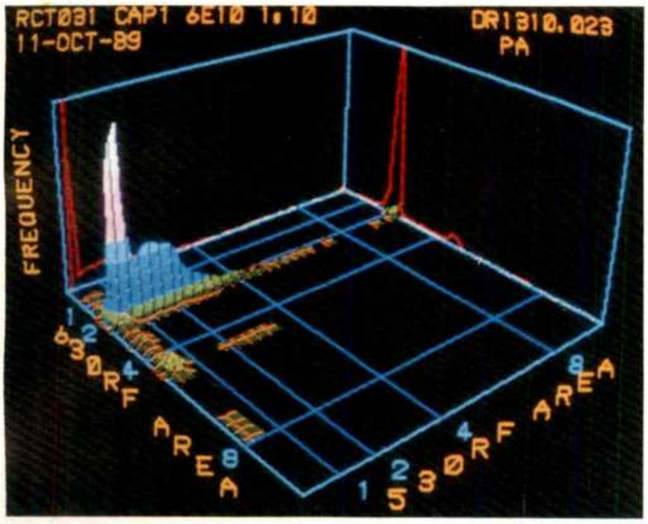

Figure 1 *Three-dimensional histogram illustrating the analysis of p62c-*myc *content by multiparameter flow cytometry. The 530 nm width plot reflects p62 c-*myc *content. The 630 RF area plot is a ploidy histogram which records the DNA content of the nuclei. Gating around the G1 and G2 diploid and aneuploid populations on the 530 nm axis allows the mean protein content to be measured, after subtracting the mean fluorescence from similar analyses from specimens from which the 6E10 antibody has been omitted*

surgical resection specimens. These tissue blocks were stored in 70 per cent ethanol at −4°C. After mechanical mincing, fragments were incubated in 8 ml porcine pepsin (Sigma, Poole, UK) solution in 0·1 M HCl at a concentration of 0·1 mg/ml at 37°C, filtered and washed in phosphate buffered saline. The concentration of nuclei was adjusted to 2×10^6/ml. Each sample was divided into two aliquots in separate vials for primary antibody and fluorescence control measurements[23].

Nuclei were incubated in 20 μl 1/10 6E10 antibody (Cambridge Research Biochemicals, Cheshire, UK) for 1 h at room temperature, washed and resuspended in 20 μl of rat anti-mouse antibody-FITC conjugate (Sigma) for 1 h. Nuclei were counterstained with 0·025 mg/ml propidium iodide (Sigma) solution. The fluorescence control nuclei were resuspended in 20 μl of phosphate buffered saline.

Analyses were carried out on the Cambridge Medical Research Council custom-built dual laser flow cytometer using methodology previously described by Watson *et al.*[23]. An Innova 70-5W argon ion laser (Coherent, Palo Alto, California, USA) was used to excite at 488 nm light wavelength. Green fluorescent light was collected at 510–560 nm and red fluorescence above 630 nm in list mode. Data for 10 000 nuclei were collected from each specimen (*Figure 1*). The mean p62c-*myc* content of each cell cycle phase in each specimen was calculated by subtracting the fluorescence control values from the 'primary antibody' values. The results were expressed in units of fluorescence in the linear range 1–1024 units. The data were analysed by the non-parametric pairs method of Mann and Whitney.

Results

Tumour biopsies were studied from 87 patients with colorectal carcinomas. There were two well differentiated, 56 moderately and 29 poorly differentiated tumour specimens; 47 specimens were diploid and 40 specimens were aneuploid. There were 51 normal mucosal specimens from terminal ileum and sites throughout the colorectum, seven specimens from two patients with polyposis coli and four specimens of villous adenomas.

A further 26 biopsies were studied from 18 tumours to assess the intratumour variation in p62c-*myc* expression. Where multiple specimens were studied, the mean values of all data were used in all other calculations. All specimens of mucosa were excised from tumour resection specimens, and were histologically normal. Colorectal mucosal specimens were between 10 and 30 cm from the primary tumour.

Six oesophageal squamous carcinomas and 18 gastric adenocarcinomas were also studied. There were 19 specimens of histologically normal gastric mucosa and seven normal squamous mucosa specimens. Mucosal specimens were between 2·5 and 10 cm from the primary tumour.

*Evidence for cell cycle related p62c-*myc *expression*

Nuclear p62c-*myc* expression increased with DNA synthesis in both tumours and mucosa, such that the mean G2 fluorescence was up to twice that associated with the G1 diploid (G1D) peak. S phase nuclei expressed intermediate values between the G1D and G2D values. G1 aneuploid p62c-*myc* content in aneuploid tumours was intermediate to these values (*Table 1*). Comparisons between specimens and groups were based on the p62c-*myc* expression measured in the G2 diploid peak.

The difference between p62c-*myc* G1D and G2D content was significant in all tissues and tumours (Mann–Whitney pairs test, $P = 0{\cdot}001$). In 13 colorectal tumour specimens the mean G2D p62c-*myc* content was <50 units (range 0–34 units) in both G1 and G2. There was no correlation between G2D p62c-*myc* content and ploidy, anatomical site (proximal or distal colon or rectum) or grade of the colorectal tumours (*Table 1*).

*p62c-*myc *content and the BrdUrd labelling index*

The BrdUrd labelling index, an *in vivo* index of proliferation, was calculated for all specimens by MFCM[22] (*Table 1*). Mucosal data tissue labelling index was obtained for both crypt and stromal cells. A broadly inverse relationship was observed between the mean tissue BrdUrd labelling index and the nuclear p62c-*myc* content in both upper and lower gastrointestinal tumours and mucosa. If p62c-*myc* were important in the regulation of proliferation, higher levels of the protein might have been expected in cells from the more rapidly proliferating tissues.

*Intratumour variation in p62c-*myc *content*

Between two and four separate biopsies from random sites in 18 colorectal tumours were analysed (*Figure 2*). The mean(range) of values is shown for each tumour. Some tumours showed a marked intersample variation in p62c-*myc*. This is

Table 1 *Mean(s.e.m.) nuclear p62c-*myc *content in units of fluorescence of the G1 and G2 diploid peaks, and the mean 5-bromo-2′-deoxyuridine labelling indices (Br LI) of oesophageal, gastric and colorectal tumours, adenomas and mucosa*

Specimens	G1D	G2D	Br LI (%)
Oesophageal (squamous)			
Carcinoma (*n* = 6)	140(49)	248(76)	6·9(2·2)
Mucosa (*n* = 7)	137(26)	238(49)	3·7(1·0)
Gastric (glandular)			
Carcinoma (*n* = 18)	144(17)	258(24)	5·8(1·3)
Mucosa (*n* = 19)	232(34)	388(36)	2·5(0·3)
Colorectal mucosa			
All (*n* = 51)	227(20)	306(24)	2·1(0·2)
Ileum (*n* = 10)	115(13)	201(20)	1·8(0·5)
Right colon (*n* = 10)	189(22)	330(38)	2·3(0·6)
Transverse colon (*n* = 8)	239(30)	369(31)	2·3(0·5)
Left colon (*n* = 8)	213(45)	315(44)	2·5(0·6)
Sigmoid colon (*n* = 8)	180(27)	279(48)	1·6(0·4)
Rectum (*n* = 7)	252(39)	346(45)	2·1(0·4)
Polyposis coli mucosa (*n* = 7)	443(93)	503(64)	2·6(0·5)
Villous adenoma (*n* = 4)	96(25)	157(58)	6·0(1·1)
Colorectal tumours			
All tumours (*n* = 87)	127(10)	188(14)	9·7(0·5)
Well differentiated (*n* = 2)	150	203	7·5
Moderately differentiated (*n* = 56)	121(9)	171(14)	9·0(0·6)
Poorly differentiated (*n* = 29)	147(19)	218(29)	10·6(0·8)
Diploid (*n* = 47)	131(16)	185(21)	9·8(0·6)
Aneuploid (*n* = 40)	121(10)	190(17)	9·8(0·7)
Right, transverse colon (*n* = 23)	119(16)	184(22)	7·6(0·8)
Left, sigmoid (*n* = 17)	119(26)	196(30)	11·8(1·6)
Rectal (*n* = 47)	133(13)	209(16)	9·9(0·6)

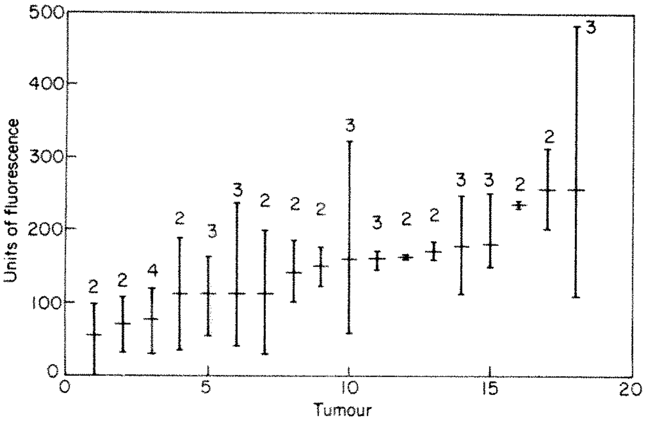

Figure 2 *Variation in the mean p62c-*myc *content of 18 colorectal tumours from which between two and four blocks were analysed. Values are mean(range). Figures above each bar represent the number of specimens analysed from that tumour*

likely to reflect tumour heterogeneity, which has also been noted for *in vivo* BrdUrd labelling in these tumours.

*Expression of c-*myc *in polyposis coli*

Seven mucosal specimens without microadenomas were studied from two patients undergoing total colectomy for polyposis coli. Nuclear p62c-*myc* content was significantly higher than the equivalent values in mucosa from colorectal tumour patients (Mann– Whitney pairs test, $P=0.001$).

Study of paired gastric tumour to mucosa specimens

Pairs of carcinoma to mucosa specimens were analysed. In only four of 18 gastric specimens and in eight of 33 colorectal pairs was the p62c-*myc* content of the mucosa lower than the corresponding tumour block (*Figure 3*). The mean G2D content of p62c-*myc* was significantly higher in both gastric and colorectal mucosa than in the corresponding adenocarcinomas ($P=0.001$) but there was no difference between the smaller series of oesophageal mucosa and squamous carcinomas (*Table 1*).

Discussion

Efforts to understand the role played by the c-*myc* gene and its protein product in the process of DNA synthesis during colorectal tumour proliferation have been complicated by the range of experimental techniques and cell models used. These variously have included the measurement of complementary DNA, messenger RNA and gene transcript levels by blotting techniques. The measurement of protein expression rather than gene transcript expression has theoretical and practical advantages. Protein content is the end point of gene expression, and is the mechanism by which gene function is effected. It is therefore likely that the measurement of protein expression using monoclonal antibodies such as 6E10 will provide another useful indicator of changed gene function and expression, being the end point of changes in gene regulation, transcription and translation.

The flow cytometric and histological study of nuclear p62c-*myc* content in paraffin embedded archival material is complicated by formalin fixation artefact. The use of 70 per cent ethanol or methanol as a preservative appears to reduce these problems[24]. Although the epitope recognized by 6E10 is believed to be resistant to pepsin, care must be taken using pepsin digestion[25].

It was found in this series that nuclear p62c-*myc* content of colorectal tumour cells does not appear to vary with histological grade, ploidy or anatomical site of origin. This finding is contrary to some previous reports. It was not possible to demonstrate a relationship between nuclear p62c-*myc* levels and cell proliferation in tumour cells as measured by BrdUrd incorporation.

The results described raise a number of questions about the role of the c-*myc* gene product in human gastrointestinal cancer. The c-*myc* gene product *as measured by the 6E10 antibody* in both tumour and mucosal cells is a protein whose quantity increases linearly with DNA content through the cell cycle. It has previously been shown that DNA binding may be a part of p62c-*myc* function through the leucine zipper mechanism. A simple doubling of mean protein content with chromosome duplication from G1D to G2D is not observed. This may reflect a partial degradation of nuclear p62c-*myc* during tumour disaggregation. It may be more appropriate to compare the *early* G1 protein content with the *late* G2 protein content.

The finding of high nuclear p62c-*myc* expression in normal gastrointestinal mucosa as compared with adenocarcinomas suggests that either the c-*myc* gene is down-regulated in malignant cells, or a higher proportion of the protein content is exported from the nucleus to the cytoplasm of tumour cells. It is clearly important that no gene is designated as an oncogene until the expression of its product has been assessed in both the tumour and in its tissue of origin. Transcriptional expression (messenger RNA products) may differ from translational expression (protein product). Conclusions about the nature of a gene should be based on studies from a number of techniques, including quantitative measurement of the protein product where possible. The protein content of malignant cells may be low despite a rise in the absolute number of gene and transcriptional copies caused by altered gene control, because of impaired protein synthesis.

The function of the c-*myc* gene remains unclear. The findings reported here would be compatible with a role for p62c-*myc* as a DNA binding structural protein, or as a gene regulatory or enzymatic protein. Immunohistochemical studies of the distribution of p62c-*myc* within tumour cells, stromal cells and mucosa have been reported[19,20,26]. The finding of p62c-*myc* in the cytoplasm of differentiated colonic crypt mucosal and tumour cells, for example, would be compatible with a role for p62c-*myc* as a differentiation regulator which was extruded from the nucleus as cells reached maturity. The role that p62c-*myc* might play in the putative sequence of changes from mucosa through adenomas to frank carcinoma is unclear.

It is possible that nuclear p62c-*myc* is differently expressed in mucosa of tumour-containing bowel than in mucosa of non-malignant bowel. There was no evidence from histological or BrdUrd proliferation studies on this material (C. S. Potten, personal communication) that our mucosal specimens were in any way different from 'non-malignant' mucosa.

The p62c-*myc* levels were high in polyposis coli mucosa but were low in the small number of villous adenomas studied. The observation of a high p62c-*myc* content in the mucosa of

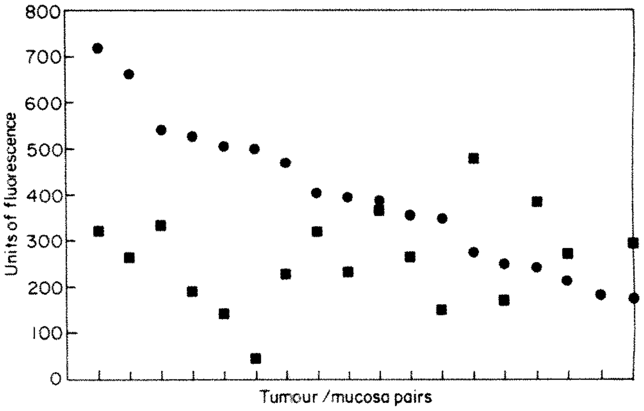

Figure 3 *Pairs of gastric mucosa and carcinoma specimens are plotted on the vertical axis to illustrate how in all but four cases the mean G2D p62c-*myc *content of the mucosa exceeds that of the carcinoma.* ●, *G2D gastric mucosa;* ■, *G2D gastric tumour*

patients with polyposis coli mandates further investigation, because it suggests that p62c-*myc* may be useful as a disease marker in polyposis coli, and may provide further clues to the role of p62c-*myc* in the process of adenoma formation in polyposis coli.

Our observations using MFCM are confined to nuclear p62c-*myc*. Cytoplasmic and cell membrane protein is lost during extraction, so it is not possible to quantify any non-nuclear protein which may be present. For this reason and because tissue architecture is destroyed by pepsin extraction, immunohistochemical studies are important. Changes in the pattern of p62c-*myc* staining in intestinal mucosa mirror the distribution of proliferating cells to some extent. Mucosal p62c-*myc* is both nuclear and cytoplasmic in distribution but becomes progressively more cytoplasmic in the zone of maturation. The changing intracellular distribution of the protein may be an important clue to function. In one model, expulsion of the protein from the nucleus may be associated with a change in the state of differentiation of the cell or tissue. Thus, surface colorectal mucosal crypt cells may have a lower nuclear to cytoplasmic p62c-*myc* ratio than do cells in the proliferation zone.

In conclusion, the studies reported in this paper support the view that the c-*myc* protein is a cellular protein of unknown function whose quantity increases with DNA synthesis, more so in mucosal than in tumour cell nuclei. The c-*myc* gene in colorectal tumour and mucosal cells may be a normal cellular gene rather than an oncogene. Multiparameter flow cytometry is a powerful tool with which to measure translational gene expression in the assay of nuclear antigens in solid tumours and tissues. The finding of high c-*myc* expression in normal gastrointestinal tissue as compared with adenocarcinomas suggests that reduced nuclear content of normal c-*myc* protein in adenocarcinomas may be an aetiological feature of gastrointestinal malignancy. The underlying mechanism and the primary function of the p62c-*myc* protein remain unclear.

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References

1. Taub RM, Moulding C, Battey J *et al.* Activation and somatic mutation in the translocated c-*myc* gene in Burkitt's lymphoma. *Cell* 1984; **36**: 339–48.
2. Rabbitts PH, Watson JV, Lamond A *et al.* Metabolism of c-*myc* gene products: c-*myc* mRNA and protein expression in the cell cycle. *EMBO J* 1985; **4**: 2009–15.
3. Studzinski GP, Brelvi ZS, Feldman SC, Watts RA. Participation of c-*myc* in DNA synthesis of human cells. *Science* 1986; **234**: 467–70.
4. Burck KB, Liu ET, Larrick JW. Myc and other nuclear oncogenes. In: Burck KB, Liu ET, Larrick JW, eds. *Oncogenes – An Introduction to the Concept of Cancer Genes*. New York: Springer, 1989: 198–221.
5. Evan G, Hancock D. Nuclear structures containing p62c-*myc*. *Cell* 1985; **43**: 253–61.
6. Evan G, Lewis GK, Ramsay G, Bishop JM. Isolation of monoclonal antibodies specific for human and mouse proto-oncogene products. *Mol Cell Biol* 1985; **5**: 3610–16.
7. Dang CV, McGuire M, Buckmire M, Lee WM. Involvement of the Leucine Zipper region in the oligomerization and transforming activity of human c-*myc* protein. *Nature* 1989; **337**: 664–6.
8. Karn J, Watson JV, Lowe AD, Green SM, Vedeckis W. Regulation of the cell cycle by c-*myc* levels. *Oncogene* 1989; **4**: 773–87.
9. Calabretta B, Kaczmarek L, Ming P, Au F, Mang S. The expression of c-*myc* and other cell cycle dependent genes in human colon neoplasia. *Cancer Res* 1985; **45**: 6000–4.
10. Vogelstein B *et al.* Genetic alterations during colorectal tumour development. *N Engl J Med* 1988; **319**: 9, 525–32.
11. Erisman MD, Scott JK, Astrin SM. Evidence that the familial polyposis coli gene is involved in a subset of colon cancers with a complementable defect in c-*myc* regulation. *Proc Natl Acad Sci USA* 1989; **86**: 4264–8.
12. Dolcetti R, De-Re V, Viel A, Pistello M, Tavian M, Boiocchi M. Nuclear oncogene amplification or rearrangement is not involved in human colorectal malignancies. *Eur J Cancer Clin Oncol* 1988; **24**: 1321–8.
13. Watson JV. Oncogenes, cancer and analytical cytology. *Cytometry* 1986; **7**: 400–10.
14. Sikora K, Chan S, Evan G *et al.* c-*myc* oncogene expression in colorectal cancer. *Br J Cancer* 1987; **59**: 1289–95.
15. Stewart J, Evan G, Watson JV, Sikora K. Detection of the c-*myc* oncogene product in colonic polyps and carcinomas. *Br J Cancer* 1986; **53**: 1–6.
16. Imaseki H, Hayashi H, Taira M *et al.* Expression of c-*myc* oncogene in colorectal polyps as a biological marker for monitoring malignant potential. *Cancer* 1989; **64**: 704–9.
17. Finley GG, Schultz NT, Hill SA, Geiser JR, Pipas JM, Meisler AI. Expression of the c-*myc* gene family in different stages of human colorectal cancer. *Oncogene* 1989; **4**: 963–71.
18. Constantini CR, Theillet C, Hutzell P, Merlo G, Schlom J, Callaghan R. *In situ* detection of c-*myc* mRNA in adenocarcinomas, adenomas and mucosa of human colon. *J Histochem Cytochem* 1989; **37**: 293–8.
19. Watson JV, Stewart J, Cox C, Sikora K, Evan GI. Flow cytometric quantitation of the c-*myc* oncoprotein in archival neoplastic biopsies of the colon. *Mol Cell Probes* 1987; **1**: 151–7.
20. Williams ARW, Piris J, Wyllie AH. Immunohistochemical demonstration of altered intracellular localisation of the c-*myc* oncogene product in human colorectal neoplasms. *J Pathol* 1990; **160**: 287–93.
21. Ten-Kate J, Eidelman S, Bosman FT, Damjanov I. Expression of the c-*myc* proto-oncogene in normal human intestinal epithelium. *J Histochem Cytochem* 1989; **37**: 541–5.
22. Rew DA, Taylor I, Wilson GD, Weaver PC. The *in vivo* proliferation kinetics of human colorectal carcinomas. *Br J Surg* 1991; **78**: 60–6.
23. Watson JV, Sikora K, Evan GI. A simultaneous flow cytometric assay for c-*myc* oncoprotein and cellular DNA in nuclei from paraffin embedded material. *J Immunol Methods* 1985; **83**: 179–92.
24. Feichter GE, Goerttler K. Pitfalls in the preparation of nuclear suspension from paraffin embedded tissue for flow cytometry. *Cytometry* 1986; **7**: 616.
25. Lincoln ST, Bauer KD. Limitations in the measurement of c-*myc* oncoprotein and other nuclear antigens by flow cytometry. *Cytometry* 1989; **10**: 456–62.
26. Sundaresan V, Forgacs IC, Wight DGD, Wilson B, Evan GI, Watson JV. Abnormal distribution of c-*myc* oncogene production in familial adenomatous polyposis. *J Clin Pathol* 1987; **40**: 1274–81.

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Nutritional status after total and partial gastrectomy with Roux-en-Y reconstruction

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Dietary intake and nutritional status were studied in two groups of patients after total gastrectomy (n = *10*) *and after partial gastrectomy* (n = *10*). *All patients were reconstructed with a Roux-en-Y loop. Investigations were carried out 4–17 years after the operation. Eight patients in the group undergoing total gastrectomy and four patients undergoing partial gastrectomy had gastric carcinoma and were without recurrent disease 5–15 years after the operation. A clinical dietician conducted an anthropometric evaluation. All patients underwent an upper gastrointestinal endoscopy, clinical examination,* $[^{14}C]$*triolein breath test and a blood chemistry profile. The median weight loss from operation to investigation was 2·1 kg in the partial gastrectomy group and 6·7 kg in the total gastrectomy group (n.s.). After partial gastrectomy three patients had a subnormal body mass index (n.s.). This was not found in the total gastrectomy group. Energy intake was below that recommended in seven patients in the partial gastrectomy group (three of them had a subnormal body mass index) and in two in the total gastrectomy group (n.s.)* $[^{14}C]$*triolein breath testing revealed fat malabsorption in three patients after partial gastrectomy and in five patients after total gastrectomy (n.s.).*

Incapacitating nutritional deficiency is often regarded as an inevitable consequence in a proportion of patients after total gastric resection. Lack of gastric reservoir capacity is thought to be one of the reasons and a variety of surgical procedures have been devised to create a gastric substitute. The benefit of these pouches compared with a simple Roux-en-Y reconstruction has been hard to demonstrate.

Most patients undergoing total gastrectomy have gastric cancer. The long-term prognosis is still poor[1–3]. To justify a more complex operative procedure in this group, evidence of short-term and long-term benefits should be provided. Short-term studies in humans and animals have not revealed any benefit with pouch formation[4–6]. In short-term studies on these patients, one difficulty is to exclude recurrence as a factor contributing to a deficient nutritional status.

To assess the benefit of a gastric pouch, the nutritional status of patients subjected to total gastrectomy 4–17 years ago was compared with a similar group after partial gastrectomy and Roux-en-Y reconstruction.

Materials and methods

Patients

Since the beginning of the 1970s patients with gastric carcinoma in the Department of Surgery, Lund University have undergone total gastrectomy with Roux-en-Y oesophagojejunostomy. In 1979, a prospective study was started on all patients subjected to total gastrectomy. Reconstruction was with a 50–60 cm Roux-loop, with the oesophagojejunostomy fashioned with a circular stapler device. Patients were followed regularly by clinical examination and, in some instances, upper gastrointestinal endoscopy. Laboratory analyses of haemoglobin, serum iron, transferrin, cobalamin and folate were performed yearly and any deficiency regulated by supplementation. All patients were recommended treatment with oral iron supplementation. Vitamin B_{12} injections were given every third month unless the patient developed very high serum values. No other vitamin supplementation was routinely prescribed.

Five years elapsed after surgery before the patient was judged free of cancer. In those subjected to total gastrectomy, only eight patients fulfilled that requirement and were included in the study. Two patients were included after total gastrectomy for benign disease. The total gastrectomy group consisted of four women and six men, with a median age of 74·5 years (range 45–81 years) operated on 4–17 years previously.

Ten consecutive patients from 36 treated by partial gastric resection between 1945 and 1962 for ulcer disease and subsequently with re-resection, Roux-en-Y gastrojejunostomy and truncal vagotomy agreed to participate and constituted the partial gastrectomy group. The one woman and nine men in this group had a median age of 73 years (range 55–78 years) and had been operated on 9–16 years earlier. Patient data are shown in *Table 1*.

Clinical examination

Patients were interviewed regarding eating habits, gastrointestinal symptoms, bowel habit, substitution medication and other diseases, and all were subjected to an upper gastrointestinal endoscopy and clinical examination. Data on diagnosis, date of operation, operative procedure, preoperative weight and previous gastric surgery were retrieved from medical records.

Table 1 *Sex, age, weight development after surgery and diagnosis*

	Total gastrectomy	Partial gastrectomy
Number	10	10
Women:men	4:6	1:9
Median age (years)	74·5 (45–81)	73 (55–78)
Median age at operation	64·5 (39–71)	60·5 (45–63)
Median time from operation to investigation (years)	7·5 (4–17)*	13 (9–16)*
Median weight loss from operation to investigation (kg)	6·7 (−17·2– +2·7)	2·1 (−8·9– +9·2)
Diagnosis at operation		
Adenocarcinoma	8	4
Leiomyoma	1	–
Reflux gastritis	–	5
Stomal ulcer	–	1
Gastric retention	1	–

Values in parentheses are ranges. * $P = 0·01$

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A clinical dietician (E.I.) performed a 4-day dietary survey and anthropometric measurements, including body-weight, height, triceps skin-fold (measured with a Harpenden caliper (British Indicators Ltd., St. Albans, Herts, UK)), arm muscle circumference and mid-arm circumference. Normal values for arm anthropometry were established by Symreng[7]. Reference values for recommended intake of nutrients were collected from the Swedish Food Administration[8]. The intake of energy and nutrients during the 4-day dietary survey was calculated from food tables from the Swedish Food Administration using a computer system[9].

Triolein breath test

After an overnight fast the patients drank 100 ml of a fat emulsion (Intralipid®, KABI Infusion, Sweden) containing soybean oil (200 mg/ml) and egg phospholipids (12 mg/ml). To the emulsion 65 kBq [^{14}C]triolein (tri-[1-^{14}C]oleoylglycerol; The Radiochemical Centre, Amersham, UK) had been added. The patients remained fasting for 6 h, and small amounts of drinking water were allowed. At 0, 2, 4, 5 and 6 h breath CO_2 was collected in liquid scintillation vials containing 2 ml 1 M hyamine: ethanol (1:1) and a few drops of phenolphthalein solution. To the samples 15 ml toluene-based liquid scintillation fluid was added. A constant endogenous CO_2 production of 9 mmol/kg body-weight per hour was assumed. The data were expressed as peak expiratory $^{14}CO_2$ (percentage of given dose per hour) or cumulative expiratory $^{14}CO_2$ (percentage per 6 h)[10,11].

Table 2 *Supplementary medication and gastrointestinal symptoms*

	Total gastrectomy	Partial gastrectomy
Number of patients	10	10
Energy supplements	1	0
Multivitamin intake	4	2
Vitamin B_{12} injections	5	1
Peroral iron medication	7	3
Early satiety	3	6
Dysphagia	1	0
Heartburn	2	1
Postprandial discomfort	1*	7*
Dumping	0	2
'Never hungry'	2	3
Meals a day		
3–5	9	9
6–8	1	0
>8	0	1
Daily stool frequency		
<1	1	1
1–2	9	7
3–4	0	2
>4	0	0
Diarrhoea	0	0
Constipation	1	1
Gas problems	4	4

* $P = 0{\cdot}02$

Statistical methods

For comparison of measurements, a normal probability plot was performed. When the data were not normally distributed the Mann–Whitney *U* test was used, otherwise Student's unpaired *t* test was applied. For nominal data the Fisher exact probability test was used because of the small numbers.

Results

Clinical examination and interview disclosed mild diabetes treated with dietary restrictions in one patient with total gastrectomy; otherwise no concomitant diseases with bearing on nutritional status were found. Patients in both groups were all in good health. A mild anaemia was detected in four patients (blood haemoglobin of 100–120 g/l) and a more pronounced anaemia in one patient (blood haemoglobin 84 g/l) after total gastrectomy. After partial gastrectomy, mild anaemia was found in two patients. Serum bilirubin and enzyme activities reflecting liver function were normal for all patients. Upper gastrointestinal endoscopy did not show any signs of recurrent disease, stricture formation, mechanical obstruction, oesophagitis or reflux gastritis in the 20 patients.

Data on eating habits, the prevalence of postprandial problems and bowel movements, as well as intake of supplementary medication and energy supplements, are listed in *Table 2*. The two groups were equal in most respects except that postprandial discomfort was more common in patients after partial gastrectomy ($P = 0{\cdot}02$, two-tailed Fisher exact test).

The weight loss after operation was not significantly different between the two groups (*Table 1*). Data on body composition

Table 3 *Anthropometric evaluation and daily energy intake*

Sex	Age (years)	Type of gastrectomy	Body mass index	Triceps skin-fold (mm)	Arm muscle circumference (cm)	Energy intake (MJ)
F	81	Total	19·2	13·4	20·7	8·3
F	70	Total	24·3	14·1	24·6	6·6
F	69	Total	20·2	15·4	19·7	9·2
F	78	Total	22·3	15·2	19·7	6·5*
M	73	Total	20·8	9·7	24·4	11·8
M	75	Total	21·3	8·1	23·4	8·4
M	74	Total	21·0	11·7	23·8	11·8
M	76	Total	21·5	6·8	25·9	10·0
M	76	Total	24·2	19·2	24·5	8·4
M	45	Total	20·6	9·7	24·0	7·7*
F	74	Partial	18·8	9·1*	19·6	5·8*
M	66	Partial	19·7*	7·6	25·1	8·4*
M	74	Partial	18·7*	6·1*	21·8*	8·2*
M	78	Partial	27·2	10·4	35·9	9·6
M	67	Partial	17·4*	4·4*	22·1*	7·7*
M	55	Partial	22·1	6·1*	25·6	9·5*
M	72	Partial	24·5	10·5	24·7	10·7
M	67	Partial	26·3	12·0	26·7	7·6*
M	75	Partial	28·6	14·4	29·7	9·6
M	77	Partial	21·7	9·5	26·5	5·8*

*Subnormal values. (Reference values were collected from References 7 and 8) and energy intake indicated that patients having undergone total gastrectomy performed just as well as, or better than, those after partial gastrectomy (*Table 3*). The median energy intake was 8·4 MJ (range 6·5–11·8) after total gastrectomy and 8·3 MJ (range 5·8–10·7) after partial gastrectomy (n.s.). In *Table 4* data on body mass index are grouped in terms of overweight, underweight and normal body-weight. After total gastrectomy, all patients were within the normal range or over, whereas after partial gastrectomy three patients were underweight.

The triolein breath test revealed a fat malabsorption in about half of the patients in both groups (*Table 5*) and expiratory $^{14}CO_2$ was somewhat lower in the total gastrectomy group.

Discussion

No long-term difference in energy intake or nutritional status in favour of the group with a gastric remnant was detected. Other studies have not demonstrated any benefit of forming a gastric pouch after total gastrectomy. Aguste *et al.*[6] made a Hunt–Lawrence pouch in one group of dogs and a Roux-en-Y reconstruction in another group, and followed the nutritional effects for 3 months. A slight nutritional benefit in animals with the Roux-en-Y reconstruction was demonstrated. The only published randomized study in humans with different reconstructions after total gastrectomy is still not concluded. An interim study did not report any obvious difference between those reconstructed with a Hunt–Lawrence–Rodino pouch compared with those with an oesophagojejunostomy[4]. Only 39 per cent of the patients survived the first postoperative year, which reflects a major problem in nutritional studies after surgery for gastric cancer. Other studies reporting short-term and long-term nutritional results in children[12] and adults[3,13,14] provide favourable results with Roux-en-Y reconstruction after total gastrectomy, if effects of recurrent disease can be excluded.

Compared with comparable Swedish cohorts, the energy intake in the total gastrectomy and partial gastrectomy groups was normal. In a study from the north of Sweden[15], the mean energy intake in 65-year-old subjects with double dental prostheses was 6·3 MJ in women and 7·7 MJ in men. In a representative subsample of 182 men and 188 women from a total of 1148 70-year-old people in a Gothenburg population study[16], the mean(s.d.) intake of energy in men was 9·8(2·5) MJ and in women 8·1(2·3) MJ.

The patients were well adjusted to their situation nutritionally as evidenced by the anthropometric evaluation, which revealed no major signs of malnutrition. In a study on nutritional effects after gastric resection, Lawrence *et al.*[17] found that the most important factor in adequate nutritional maintenance seemed to be the ability to control postprandial symptoms. The higher frequency of postprandial symptoms among patients with partial gastrectomy may explain their lower anthropometric values and energy intake.

A substantial proportion of patients in both groups had fat malabsorption, revealed by the triolein breath test. The reason for this effect is unclear[5]. Reduced pancreatic function due to duodenal exclusion, an insufficient mixing of food and digestive juices, a rapid passage through the intestine, and an increased and altered bacterial flora in the small intestine have all been invoked as contributing factors.

Lawrence *et al.*[17] and Walther *et al.*[18] found that over 80 per cent of their patients initially had an abnormal fat absorption after total gastrectomy. Faecal fat losses decreased with time when the digestive system readjusted to the new situation[17]. Fat absorption in both study groups was closer to normal than that measured with the same method in patients 1 and 6 months after total gastrectomy[18]. The prevailing hypothesis is that faecal fat losses are mainly a result of loss of duodenal passage for chyme[19]. Steatorrhoea has, however, been found in 67 per cent of patients after total gastrectomy reconstructed with jejunal interposition between the oesophagus and duodenum[20], and comparing two groups of patients after gastrectomy reconstructed with and without duodenal passage Siewert *et al.*[21] could not find any difference in fat malabsorption, which implies that other factors are also involved.

It is acknowledged that the two groups in this study represent a selection of long-term survivors who have overcome their underlying disease. In addition, patients with major problems of a technical nature linked to the operative procedure were presumably excluded after this long follow-up. It is of great importance not to create a stricture when forming the anastomosis between the oesophagus and jejunum. Present knowledge regarding weight-reducing operations in morbid obesity indicates that if only the reservoir function of the stomach is taken away malnutrition will not appear even if a pouch as small as 40 ml is left, whereas if the outlet of the stoma is too narrow a high proportion of patients will develop malnutrition[22].

The good health and nutritional status observed after total gastrectomy implies that a surgical technique which prevents bile reflux and stricture formation is probably of the greatest importance. The creation of a new gastric pouch is probably of less importance for the long-term nutritional effects after total gastrectomy.

Table 4 *Body mass index**

	Underweight	Normal	Overweight
Total gastrectomy	–	9	1
Partial gastrectomy	3	4	3

* Weight (kg)/height^2 (m^2)

Table 5 *Fat malabsorption after gastrectomy, studied by the [^{14}C]triolein breath test*

			Expiratory $^{14}CO_2$	
	Subnormal	Normal	Peak value (%/h)*	Cumulative (%/6 h)†
Total gastrectomy	5	5	3·0 (1·3)	10·6 (3·2)
Partial gastrectomy	3	7	4·0 (1·4)	14·7 (4·5)‡

* Reference values 2·8–7·5%/h. † Reference values 8·6–25·0%/6 h. ‡ Significantly different from total gastrectomy group ($P < 0·05$). Values in parentheses represent standard deviation from the mean

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References

1. Zilling TL, Willén R, Walther BS, Ranstam J. Prediction of survival in gastric carcinoma and a new histopathologic approach. *Anticancer Res* 1989; **9**: 487–500.
2. Lundegårdh G, Adami H-O, Malker B. Gastric cancer survival in

Sweden. Lack of improvement in 19 years. *Ann Surg* 1986; **204**: 546–51.
3. Schrock T, Way L. Total gastrectomy. *Am J Surg* 1978; **135**: 348–55.
4. Troidl H, Kusche J, Vestweber K-H, Eypasch E, Maul U. Pouch versus esophagojejunostomy after total gastrectomy: a randomised clinical trial. *World J Surg* 1987; **11**: 699–712.
5. Bradley E, Isaacs J, Hersh T, Davidson E, Millikan W. Nutritional consequences of total gastrectomy. *Ann Surg* 1975; **182**: 415–29.
6. Aguste L, Mavor E, Citrin P, Stein T, Mandell C, Wise L. Nutritional effects of postgastrectomy reconstructions. *Am J Surg* 1985; **150**: 537–42.
7. Symreng T. Arm anthropometry in a large reference population and in surgical patients. *Clinical Nutrition* 1982; **1**: 211–19.
8. Swedish Food Administration. *Svenska näringsrekommendationer SNR*. 2nd ed. Uppsala, 1989: 5 pp (in Swedish).
9. Swedish Food Administration, SLV. *Livsmedelstabeller*. Uppsala, 1986 (in Swedish).
10. Newcomer A, Hofman A, DiMagno E, Thomas P, Carlson G. Triolein breath test. A sensitive and specific test for fat malabsorption. *Gastroenterology* 1979; **76**: 6–13.
11. Åkesson B, Florén C-H. Use of the triolein breath test for the demonstration of fat malabsorption in coeliac disease. *Scand J Gastroenterol* 1984; **19**: 307–14.
12. Wilson S, Ellison E. Total gastric resection in children with the Zollinger–Ellison syndrome. *Arch Surg* 1965; **91**: 165–73.
13. Cristallo M, Braga M, Agape D *et al.* Nutritional status, function of the small intestine and jejunal morphology after total gastrectomy for carcinoma of the stomach. *Surg Gynecol Obstet* 1986; **163**: 225–30.
14. Koga S, Nishimura O, Iwai N *et al.* Clinical evaluation of long term survival after total gastrectomy. *Am J Surg* 1979; **138**: 635–9.
15. Söremark R, Nilsson B. Dental status and nutrition in old age. In: Carlson LA, ed. *Symposium of the Swedish Nutrition Foundation X: Nutrition in Old Age*. Uppsala: Almqvist and Wiksell, 1972: 147.
16. Steen B, Isaksson B, Svanborg A. Intake of energy and nutrients and meal habits in 70-year-old males and females in Gothenburg, Sweden. A population study. *Acta Med Scand* 1977; **611**(Suppl): 39–81.
17. Lawrence W, Vanamee P, Peterson A, McNeer G, Levin S, Randall H. Alterations in fat and nitrogen metabolism after total and subtotal gastrectomy. *Surg Gynecol Obstet* 1960; **11**: 601–16.
18. Walther B, Clementsson C, Vallgren S, Ihse I, Åkesson B. Fat malabsorption in patients before and after total gastrectomy studied by the triolein breath test. *Scand J Gastroenterol* 1989; **24**: 309–14.
19. Bradley III E, Isaacs J, Del Mazo J, Hersh T, Chey W. Pathophysiology and significance of malabsorption after Roux-en-Y reconstruction. *Surgery* 1977; **81**: 684–91.
20. Gullo L, Costa P, Ventrucci M, Mattioli S, Viti G, Labo G. Exocrine pancreatic function after total gastrectomy. *Scand J Gastroenterol* 1979; **14**: 401–7.
21. Siewert J, Schattenmann G, Ebert R. Importance of the duodenal passage following gastrectomy. In: Herfarth C, Schlag B, eds. *Gastric Cancer*. Berlin: Springer, 1979: 237–41.
22. MacLean L, Rhode B, Shizgal H. Nutrition following gastric operations for morbid obesity. *Ann Surg* 1983; **198**: 347–55.

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A more physiological alternative to total fundoplication for the surgical correction of resistant gastro-oesophageal reflux

The incidence of mechanical complications associated with the Nissen fundoplication has prompted evaluation of an anti-reflux procedure designed to be simpler and more physiological, and encompassing a broader view of the many factors involved in the anti-reflux mechanism. Preliminary assessment of the first 100 patients with a mean follow-up of 3·5 years showed symptomatic improvement in 96 per cent and complete relief in 85 per cent. A further 100 patients were studied using formal symptom scoring, endoscopy, manometry and pH monitoring performed before operation and 3 months after operation. Similar clinical results were accompanied by improvement in endoscopic oesophagitis in 95 per cent, complete healing in 74 per cent and restoration of the pH profile to physiological levels in 84 per cent. Troublesome mechanical complications comprised a 2 per cent incidence of dysphagia, but there was no gas bloat or inability to belch or vomit, which may relate to the restoration of lower oesophageal sphincter characteristics close to those of 30 asymptomatic controls. The procedure is simpler to perform than total fundoplication, is well tolerated and is applicable to patients with reflux stricture and impaired oesophageal body motility. The results of this study support the hypotheses that effective reflux control can be achieved without total fundoplication by attention to several factors of known relevance to the anti-reflux mechanism, and that restoration of characteristics of the lower oesophageal sphincter close to physiological levels results in a lower incidence of mechanical complications.

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The ideal anti-reflux procedure should be safe, effective, durable, relatively simple to perform and teach, and free from troublesome mechanical complications. The large number of procedures, together with their various modifications, that have been described since Allison's classic paper in 1951[1] highlight the difficulty in fulfilling these objectives. Although the Belsey Mark IV, Hill repair and the Nissen fundoplications are all of proven efficacy, the enthusiastic response accompanying the introduction of the Angelchik anti-reflux prosthesis[2] illustrates the support for the concept of a simple anti-reflux procedure which can be performed transabdominally.

The Nissen fundoplication is the most widely used anti-reflux procedure, and its efficacy is well documented in the treatment of resistant gastro-oesophageal reflux[3,4]. Its success, however, is frequently compromised by troublesome mechanical complications such as the gas-bloat syndrome, inability to belch or vomit, and dysphagia: complications that may reflect the production of a supracompetent lower oesophageal sphincter[5] which relaxes imperfectly on swallowing. Other complications such as slippage and disruption may necessitate reoperation[6]. The overall incidence of postfundoplication problems has recently been shown to be 28 per cent[7].

This paper describes an alternative anti-reflux procedure, which is designed to be more physiological than total fundoplication by taking into account the many factors contributing to the anti-reflux mechanism and placing less emphasis on attempts to increase lower oesophageal sphincter pressure. The study also assesses the influence of such an approach on the incidence of mechanical complications.

Patients and methods

The study was conducted in two parts. Initially, a preliminary clinical study comprised the first 100 patients who underwent the 'physiological' anti-reflux procedure between 1975 and 1979. Patients were assessed up to 5 years after operation. Subsequently, a clinical and objective study incorporating endoscopy, manometry and pH monitoring involved 100 patients undergoing anti-reflux surgery between 1985 and 1988.

Patients

Preliminary clinical study. The first 100 patients undergoing the 'physiological' anti-reflux procedure ranged in age from 22 to 74 years (mean 58·5 years) and had a female:male ratio of 1·3:1. The indications for anti-reflux surgery were: (1) intractable symptoms due to endoscopically demonstrated gastro-oesophageal reflux after an adequate trial (minimum 6 months) of standard conservative measures ($n = 56$); (2) established complications of reflux oesophagitis where no contraindication to surgery existed ($n = 44$). These comprised stricture ($n = 30$), Barrett's oesophagus ($n = 22$), ulcer ($n = 9$) and severe anaemia ($n = 5$).

Clinical and objective study. The 100 patients who underwent anti-reflux surgery in this part of the study had documented resistant gastro-oesophageal reflux without stricture formation and agreed to undergo preoperative and postoperative manometry and pH monitoring. The age range was 18–78 years (mean 53·8 years), and there was a female preponderance of 1·1:1. The indications for anti-reflux surgery in these patients were: (1) intractable reflux symptoms associated with endoscopically demonstrated oesophagitis, after exclusion of non-reflux causes, and persisting after an adequate trial (minimum 6 months) of standard conservative measures ($n = 84$);

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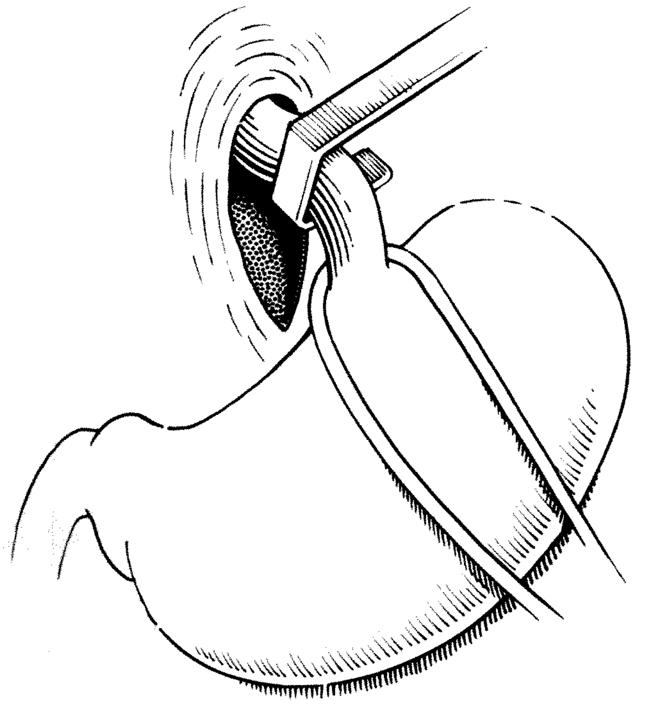

Figure 1 *Retraction of a long intra-abdominal segment of oesophagus to expose the crural sling*

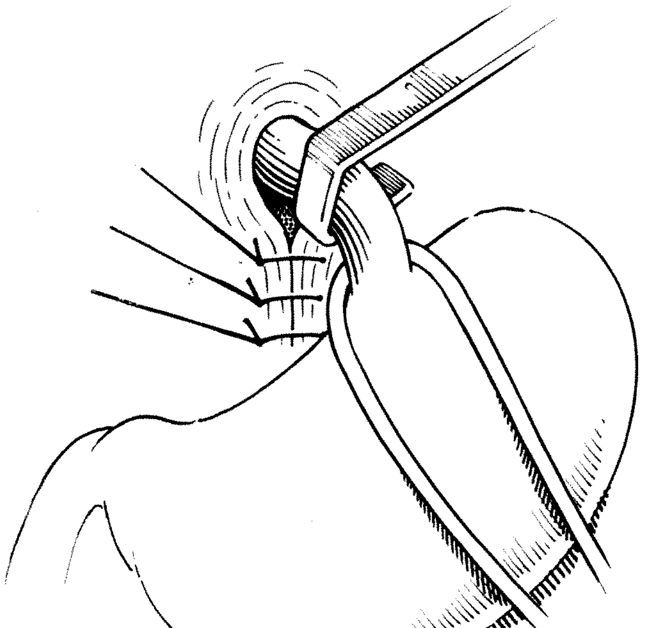

Figure 2 *Repair of the attenuated crural sling with 2/0 silk sutures. The sutures are retained and used to fix the intra-abdominal segment of the oesophagus to the crural repair*

(2) intractable symptoms suggestive of gastro-oesophageal reflux without endoscopic oesophagitis but with obvious endoscopic reflux or abnormal pH based on the study of 30 asymptomatic volunteers ($n = 8$); (3) complications of reflux oesophagitis including ulcer, Barrett's oesophagus or anaemia, but excluding stricture sufficient to prevent the passage of a standard 10 mm endoscope ($n = 8$).

Seventy-one patients had an anatomical hiatal hernia demonstrated at endoscopy, and of the patients with uncomplicated oesophagitis 36 had grade I, 36 grade II and 12 grade III oesophagitis according to the classification of Savary *et al.*[8].

Thirty asymptomatic volunteers also underwent oesophageal manometry and pH monitoring to act as controls, their age range being 21–74 years (mean 34·6 years) and sex ratio female:male 1·5:1.

Methods

Operative procedure. The objectives of the anti-reflux procedure performed were: to place and fix most (and at least 2 cm) of the lower oesophageal sphincter below the diaphragm and therefore under the influence of positive intra-abdominal pressure; to produce an effective flap valve to augment lower oesophageal sphincter tone; to utilize increases in intragastric pressure (during which reflux episodes usually occur) to augment the anti-reflux barrier; and to achieve these objectives as simply, safely and physiologically as possible with the aim of reducing the potential for mechanical complications.

In 184 patients the procedure was performed transabdominally through an upper midline incision. In 16 patients with oesophageal shortening due to extensive perioesophagitis, a left thoracoabdominal approach was used.

The phreno-oesophageal ligament was exposed by retraction of the left lobe of the liver, and divided. The plane behind the oesophagus was achieved and gentle traction applied to a Silastic® (Dow Corning, Reading, UK) sling passed around the oesophagus. By gentle blunt transhiatal dissection and division of perioesophageal adhesions if necessary, the distal oesophagus was mobilized to enable reduction of the hiatal hernia, when present, and the creation of a 4–6 cm length of intra-abdominal oesophagus. The intra-abdominal segment, together with the posterior vagus nerve, was then retracted arteriorly using a Kocher's retractor to expose the usually attenuated crural sling (*Figure 1*). The crural sling was then repaired with interrupted 2/0 silk sutures placed posterior to the oesophagus, so that only the tip of the index finger could pass along the oesophagus through the refashioned hiatus (*Figure 2*). The needles of these sutures were retained and, using the same sutures, the intra-abdominal segment of oesophagus was fixed to the crural repair by suturing the posterolateral aspect of the muscular layer of the oesophagus to the crural sling repair, avoiding the retracted posterior vagus nerve (*Figure 3*). The angle of His was reconstituted by placing interrupted silk sutures between the seromuscular layer of the superomedial aspect of the fundus of the stomach and the inferior surface of the diaphragm. A 120° anterolateral fundoplication was performed using 2/0 silk sutures between the medial aspect of the gastric fundus and the anterior aspect of the muscular layer of the oesophagus, taking care to avoid branches of the anterior vagus nerve (*Figure 4*).

The procedure was accomplished without mobilizing the gastric fundus or dividing the basa brevia or the left triangular ligament of the liver. As a result, it was performed relatively easily and expeditiously, with a mean operating time in transabdominal cases of 39 min (range 22–56 min). Patients were commenced on oral fluids on the day of operation, and the nasogastric tube was removed on the morning after operation. Feeding was commenced on the second postoperative day, and patients were discharged home usually on the fifth or sixth day after operation.

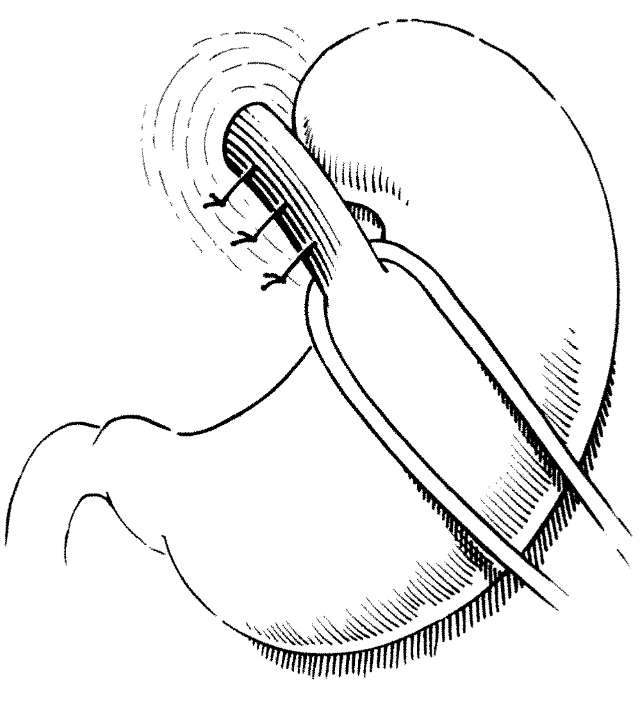

Figure 3 *The intra-abdominal segment is sutured to the crural repair*

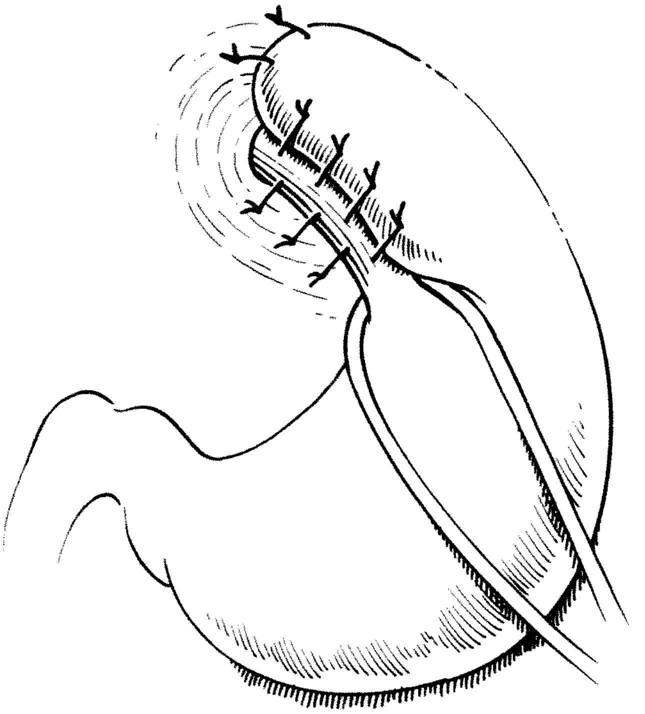

Figure 4 *The completed procedure after accentuation of the angle of His and 120° anterolateral fundoplication*

Preliminary clinical study

A postal questionnaire was sent to the 100 patients 1·4–5·5 years (mean 3·6 years) after anti-reflux surgery. It was kept simple, with the aim of assessing the effect of the operation on the alleviation of symptoms. Patients were asked to indicate whether their preoperative symptoms were absent or considerably improved, improved, unchanged, or worse. Morbidity, mortality and hospital stay were recorded.

Subsequent clinical and objective study

A formal clinical assessment, together with endoscopy, manometry and pH monitoring was performed before and 3 months after operation. The manometric and pH data were compared with those obtained in the 30 asymptomatic controls.

Symptomatic assessment. This was conducted using a scoring system which incorporated the symptoms of heartburn, regurgitation, chest pain and dysphagia, allocating each a score of 0–5 to reflect increasing severity. The presence or absence of bloating and difficulty in eructation were also noted. The symptomatic assessment was conducted by the same non-surgical observer (T.L.N.) in each case, and the total preoperative symptom score was compared with that obtained after operation.

Upper gastrointestinal endoscopy. Endoscopy was performed using an Olympus GIFQ10 endoscope (Olympus Keymed, Southend, UK) under sedation (intravenous Diazemuls® (Dumex, Princes Risborough, UK) 10–30 mg) plus local pharyngeal analgesia using benzocaine lozenges or xylocaine spray.

The presence of oesophagitis was noted and graded according to the system of Savary *et al.*[8]. Hiatal hernia or reflux and the apparent competence of the cardia during lower oesophageal sphincter contraction were also noted. Endoscopies were performed by surgical research fellows not involved in the operative procedures (L.R.J., C.S.B. and A.P.B.), and in most cases preoperative and postoperative endoscopy was performed by the same endoscopist.

Oesophageal manometry. Manometry was performed using a triple-lumen, water-perfused catheter with lumens of 0·9 mm internal diameter arranged circumferentially at 120° to each other and 5 cm apart. The catheters were perfused with sterile water at a constant rate of 0·6 ml/min by means of a low-compliance pneumohydraulic capillary infusion system at a pressure of 15 p.s.i. The station pull-through technique using 1 cm stations was employed, and pressure changes were monitored by transducers connected to a multichannel recording and display system. Swallowing and respiratory excursions were monitored by strain gauges placed around the neck and chest respectively and connected to vacant channels on the multichannel recorder.

The characteristics of the lower oesophageal sphincter studied were mean barrier pressure (calculated as a mean of 30 readings), length, length and proportion below the respiratory inversion point, and percentage relaxation to baseline on swallowing.

pH monitoring. Twenty-four hour pH monitoring was performed on an ambulatory basis under standardized dietary conditions[9], all medication having been discontinued 48 h before the study. A pH electrode was sited 5 cm above the proximal margin of the manometrically determined lower oesophageal sphincter, and a silver–silver chloride reference electrode was applied to the right upper chest wall. The electrodes were connected to a portable solid state recording system and calibrated using standard buffers at pH 1 and 7 at 25°C. During the monitoring period, sampling occurred at 4-s intervals, and the data were stored in the recorder, which incorporated an event marker to record such events as the onset of symptoms and change of posture during a prescribed schedule of 16 h upright and 8 h supine. Smoking and ingestion of alcohol or acidic foods were not permitted during the study period.

At the end of the recording period, the data were analysed for number of reflux episodes during which intraoesophageal pH was less than 4, number of reflux episodes lasting more than 5 min, duration of the longest reflux episode, and the time and percentage of the study period for which pH was less than 4, subdivided into time spent upright and supine, using the scoring system of Johnson and DeMeester[10], which apportions relative weighting to each of the above parameters. For simplicity, the percentage of total time for which the pH was below 4 and the DeMeester score were the parameters used to compare preoperative and postoperative pH status.

The criteria used to assess postoperative control of gastro-oesophageal reflux were 5 per cent or less of total time with pH <4 and DeMeester score[9] of less than 18.

Statistical analysis

In the analysis of lower oesophageal sphincter characteristics, Student's *t* test for paired data was used to determine significance between preoperative and postoperative values, and Student's *t* test for unpaired data to determine significance between postoperative and control values.

The Wilcoxon matched pair rank sum analysis was used to determine significance between preoperative and postoperative and control values for pH data, as the frequent zero values resulted in a skewed distribution, not amenable to standard statistical transformation processes.

Data relating to patient characteristics, symptom score and endoscopic grading are expressed as means and standard deviations. Those relating to manometric and pH criteria are expressed as means and 95 per cent confidence intervals.

Results

Preliminary clinical study

A response was received from 89 of the 100 patients to whom the questionnaire was sent: 75 patients (84 per cent) indicated that their preoperative symptoms were relieved or considerably improved following operation, and a further 11 (12 per cent) stated that their symptoms were improved. Three patients (4 per cent) felt that their symptoms were unchanged, and none stated that their symptoms were worse after operation. Thus 96 per cent of patients claimed that surgery relieved symptoms.

There was no mortality. Morbidity was 3 per cent: one pulmonary embolus, one subphrenic abscess and one wound dehiscence. Mean hospital stay was 7·4 days (range 5–20 days).

Clinical and objective study

There was no mortality. Morbidity was 4 per cent: one wound dehiscence, one severe chest infection and two patients who developed troublesome dysphagia requiring dilatation. Gas bloat or inability to belch or vomit did not develop. There was no incidence of splenic trauma and no mechanical sequelae necessitating reoperation. Mean hospital stay was 6·9 days (range 4–18 days).

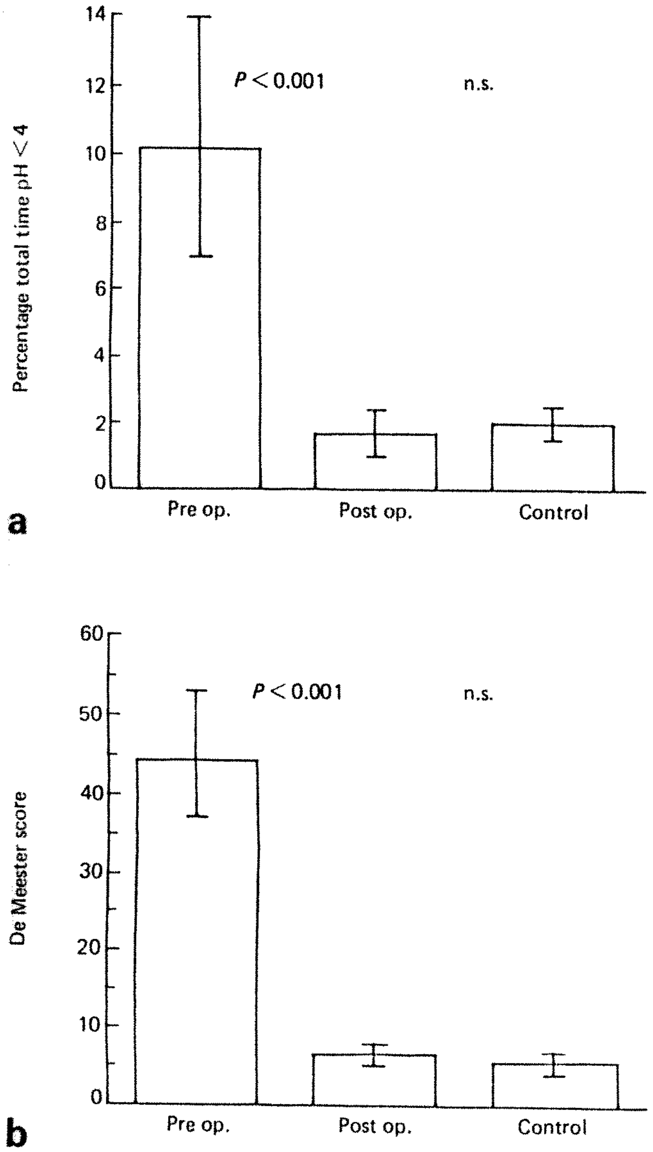

Figure 5 *pH data expressed as* **a** *percentage of total time with pH <4 and* **b** *DeMeester score before and after operation, and in 30 control subjects, shown as mean values with 95 per cent confidence intervals*

Symptom assessment. Improvement of symptoms occurred in 94 patients and total symptomatic cure in 82. The mean(s.d.) symptom score fell from a preoperative value of 3·8(1·2) to 0·8(1·0), ($P<0·005$). In 12 patients, marked dysphagia was a predominant preoperative symptom. Dysphagia resolved following operation in nine, improved in one and persisted in two patients who had associated severe motility disturbances.

No one complained of excessive or increased bloating or inability to belch or vomit. Eleven patients had transient dysphagia for solids, which resolved spontaneously within 4–6 weeks. Two patients had troublesome dysphagia which did not resolve spontaneously, and endoscopic dilatation was necessary.

Endoscopic assessment. All 100 patients underwent preoperative endoscopy. There was no evidence of endoscopic oesophagitis in eight patients, and 25 declined repeat endoscopy, leaving 67 patients with oesophagitis for comparison.

Improvement in endoscopic oesophagitis occurred in 61 (91 per cent) and healing in 50 (75 per cent). The mean grade of oesophagitis fell from 1·9(0·8) before to 0·4(0·7) after operation ($P<0·005$). Of the 17 patients in whom oesophagitis had not healed, five had grade IV oesophagitis; three of these had Barrett's columnarization, which was unchanged, and two had oesophageal ulcer, which had healed in each case. One patient with grade III oesophagitis had only improved to grade II by 3 months, and the remaining 11 patients had mild erythematous oesophagitis (grade I) at 3 months.

pH monitoring. In control subjects, the mean percentage of total time with pH <4 was 2·0(2·1) and mean De Meester score was 5·9(6·3). These values are comparable to those found by Johnson and De Meester[10].

Using percentage of total time at pH <4 of 5 per cent and De Meester score of 18 as the upper limits of normality, reflux control was achieved in 84 of the 100 patients. The mean percentage total time at pH <4 fell from 10·2(3·7) before operation to 1·7(0·7) after ($P<0·001$); mean De Meester score fell from 44·3(7·3) to 5·9(1·3) ($P<0·001$) (*Figure 5*).

Lower oesophageal sphincter characteristics. In those patients with objectively demonstrated reflux control, mean resting pressure in the lower oesophageal sphincter rose from 9·4(1·2) mmHg to 11·2(1·3) mmHg ($P<0·01$). However, this was less than the mean of 15·4(2·1) mmHg in the control group. There was no significant difference in length before and after operation (3·4(0·2) cm; 3·5(0·2) cm respectively), both being similar to control values (3·5(0·3) cm; n.s.) (*Figure 6*).

The mean length of sphincter below the respiratory inversion point increased from 1·6(0·2) cm to 2·4(0·2) cm ($P<0·001$), which is comparable to control values (2·2(0·3) cm). The proportion below the respiratory inversion point increased from a mean of 48·6(6·4) per cent before to 68·3(5·2) per cent after operation ($P<0·001$), comparable to control values (64·4(7·3) per cent; n.s.) (*Figure 7*).

The ability of the lower oesophageal sphincter to exhibit greater than 80 per cent relaxation to baseline was present in 68 (81 per cent) before and 74 (88 per cent) after operation, compared with 25 of 30 (83 per cent) in controls (n.s.) (*Figure 8*).

Discussion

Reports of the efficacy of anti-reflux procedures vary according to the author, the procedure employed and the criteria used to measure success. The Nissen fundoplication has been widely studied, giving symptomatic improvement of 65–96 per cent[3,11] and complete symptomatic relief in 35–91 per cent of cases[3,12] with return to normal pH parameters in 83–85 per cent[3,4]. Comparative studies have shown the Hill and Belsey repairs to be slightly less effective than the Nissen fundoplication[13].

Unfortunately, the success of anti-reflux procedures is frequently compromised by an appreciable incidence of mechanical complications, resulting in either troublesome postoperative symptoms or the necessity for reoperation[6,14]. These problems relate most frequently to the Nissen fundoplication and the Angelchik prosthesis. The Nissen fundoplication, with its modification by Donahue and Bombeck[15], is the procedure currently practised most widely, but it is associated with an appreciable incidence of mechanical complications[6,7,16]. The Angelchik prosthesis appears to be successful in the control of reflux symptoms[12], but this too is frequently associated with a high incidence of mechanical complications and reoperation rates of up to 20 per cent[17,18].

The advent of oesophageal manometry and pH monitoring has facilitated objective assessment of anti-reflux surgery and thrown some light on the mechanism of action of anti-reflux procedures[19,20] and the relationship of these results to the physiological state in control subjects[3]. Objective studies have shown that the Nissen fundoplication frequently results in a supracompetent lower oesophageal sphincter, which relaxes imperfectly on swallowing[5]. It appears likely that mechanical complications such as troublesome dysphagia and gas bloat are a direct consequence of these phenomena. Although attention has been directed towards the role of the lower oesophageal sphincter in the anti-reflux barrier, there is evidence to suggest that it is one of a complex of factors

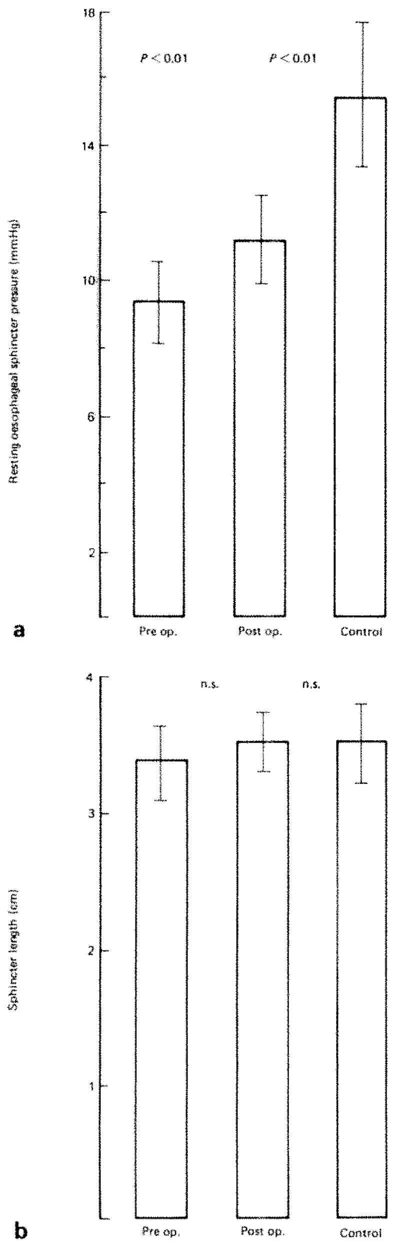

Figure 6 *Resting lower oesophageal sphincter pressure* **a** *and sphincter length* **b** *before and after operation and in 30 control subjects, shown as mean values with 95 per cent confidence intervals*

maintaining gastro-oesophageal competence. Resting lower oesophageal sphincter tone correlates poorly with reflux status[21], and surgical correction of reflux is not directly related to change in resting pressure[4,19]. Total competence has been demonstrated in the absence of the myogenic influence of the lower oesophageal sphincter in animals[22], humans[23] and even in the autopsy room[24]. Other factors, such as the length of intra-abdominal oesophagus[25], the flap-valve effect of the acute angle of His and the mucosa rosette[26] and the gastric sling fibres[27] are also important in the anti-reflux barrier. These factors can compensate for deficiency in the lower oesophageal sphincter[19,28], suggesting the potential for reflux control without mechanical complications associated with the production of a supracompetent lower oesophageal sphincter or prosthetic insertion.

The procedure we have described encompasses the various factors known to increase competence, placing emphasis on mechanical factors rather than attempts to create a highly competent lower oesophageal sphincter. The concept of increased intragastric pressure being directed to the advantage of competence is utilized by performing a 120° anterolateral fundoplication, which results in buttressing of the long intra-abdominal segment to the crural repair during gastric distension. Our results show that by incorporating these other mechanical factors, this degree of fundoplication is sufficient to produce competence without raising lower oesophageal sphincter pressure above control values or compromising lower oesophageal sphincter relaxation. We believe that these factors are relevant to the considerably reduced incidence of mechanical complications and the ability to apply the procedure to patients with stricture and disordered motility[29], in which patients many workers avoid total fundoplication.

We believe that the initial impression of the efficacy of the anti-reflux procedure described in the preliminary clinical study has been confirmed by the more recent clinical and objective study; the objective correction of reflux on pH monitoring and the healing of endoscopic oesophagitis compare favourably with other studies (*Table 1*). The healing rate of 74 per cent increased to 86 per cent at 6 months in a subsequent study of a smaller group[30]. Study at 3 months after operation is relatively early, but in the evaluation of a new procedure it is necessry to document objective parameters at a relatively early stage in

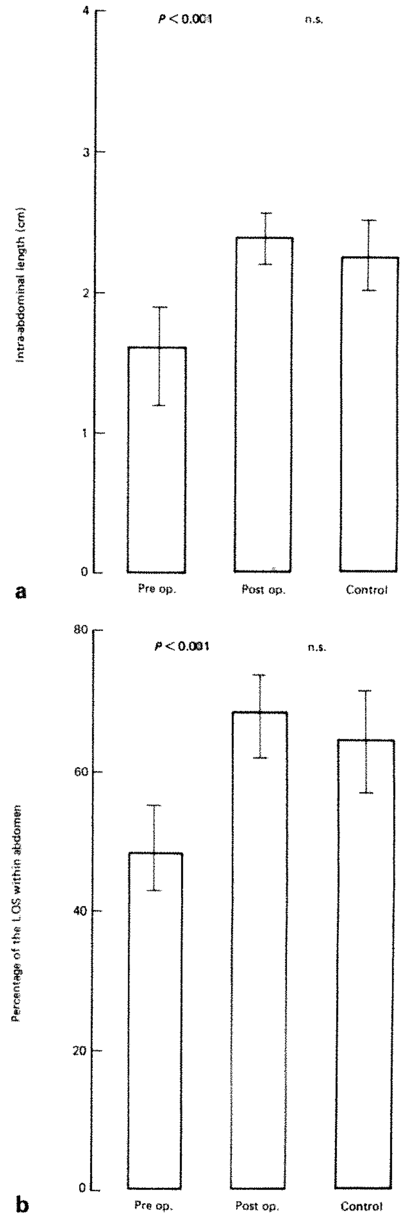

Figure 7 *Intra-abdominal length* **a** *and proportion of the lower oesophageal sphincter (LOS) within the abdomen* **b**, *shown in the same format as* Figure 6

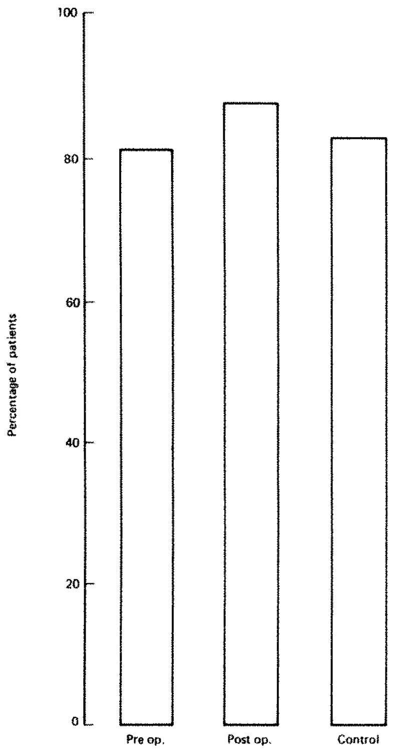

Figure 8 *Proportion of patients exhibiting greater than 80 per cent relaxation of the lower oesophageal sphincter to baseline, before and after operation, and in 30 control subjects*

Table 1 *'Physiological' anti-reflux procedure: clinical results*

Symptomatic improvement	Symptomatic cure	Healing of oesophagitis	Restoration of normal pH profile
94 (65–96)	82 (32–80)	74 (63–91)	84 (83–85)

The values shown are percentages; values in parentheses are the range recorded in the literature for the Nissen fundoplication[3,4,11,12]

Table 2 *'Physiological' anti-reflux procedure: mechanical complications*

Gas bloat syndrome	Inability to belch or vomit	Transient dysphagia	Troublesome dysphagia
0 (11–54)	0 (5–50)	11 (19–86)	2 (4–24)

*The values are percentages; values in parentheses are the ranges recorded in the literature for the Nissen fundoplication[3,5,7,16]

order to justify continued use of the procedure. However, many believe that if anti-reflux procedures fail they do so early or do not correct reflux *ab initio*; the excellent symptomatic response up to 5 years obtained in the preliminary clinical study would tend to support this impression. Furthermore, over the period 1975–1990, the senior author has conducted 452 anti-reflux procedures from a well-defined catchment area serving a population of 200 000, as well as more distant referrals. Of these patients, 17 (3·8 per cent) have required further surgery for recurrent reflux, providing further supportive evidence of durability of the procedure. We appreciate the need to document long-term objective reflux control (despite the paucity of published data on existing procedures). We are extending the study to perform endoscopy and pH monitoring at yearly intervals on consenting patients in order to provide such information.

Although the procedure described compares favourably with alternative operations, we believe its principal advantages are relative ease of performance, safety and relative freedom from mechanical complications. The procedure can be performed transabdominally in most cases, a distinct advantage over the Belsey procedure. Unlike the Nissen fundoplication, mobilization of the gastric fundus and division of the vasa brevia, with the attendant risk of splenic damage, are not required. These factors shorten operative time considerably, as do the fixation of the oesophagus rather than the gastric fundus to the crural repair, the latter being an easily visible structure as opposed to the median arcuate ligament, which many find difficult to identify and to suture safely. These factors contribute also to the relative ease of teaching the procedure to surgical trainees. While most procedures in this series were performed by the senior author, many were conducted by trainees, with comparable results. No patient required reoperation for complications and the incidence of gas bloat, inability to belch or vomit and dysphagia was considerably lower than that reported following total fundoplication (*Table 2*). We believe that these data relate to the more physiological nature of the procedure, restoring lower oesophageal sphincter characteristics, and particularly the ability to relax on swallowing, close to control values.

Although there are several effective operations for the control of resistant gastro-oesophageal reflux, each with their dedicated advocates, there remains a need to make anti-reflux surgery simpler, safer and associated with fewer side effects. We believe that this study shows that the procedure described goes some way towards fulfilling these objectives.

Acknowledgements

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References

1. Allison PR. Reflux oesophagitis, sliding hiatus hernia and the anatomy of repair. *Surg Gynecol Obstet* 1951; **92**: 419–31.
2. Angelchik JP, Cohen R. A new surgical procedure for the treatment of gastroesophageal reflux and hiatal hernia. *Surg Gynecol Obstet* 1979; **148**: 246–8.
3. DeMeester TR, Bonavina L, Albertucci M. Nissen fundoplication for gastro-esophageal reflux disease. *Ann Surg* 1986; **204**: 9–20.
4. Bancewicz J, Mughal M, Marples M. The lower oesophageal sphincter after floppy Nissen fundoplication. *Br J Surg* 1987; **974**: 162–4.
5. DeMeester TR, Johnson LF. Evaluation of the Nissen anti-reflux procedure by esophageal manometry and 24 hour pH monitoring. *Am J Surg* 1975; **129**: 94–100.
6. Leonardi HK, Corzier RE, Ellis FH. Re-operation for complications of the Nissen fundoplication. *J Thorac Cardiovasc Surg* 1981; **81**: 50–6.
7. Beauchamp G, Dube M, Perrault J. The post-Nissen fundoplication syndrome. *Proceedings 4th World Congress International Society for Disease of the Esophagus*. 1989: 55.
8. Savary M, Monnier Ph, Miller G. Diagnosis and pathophysiology of Barrett's oesophagus. In: Von Heuklem HS, Gooszen HG, Terpstra JL, Belsey RHR, eds. *Pathological Gastro-oesophageal Reflux*. Amsterdam: Zuid-Nederlands Uitg Mij. 1983: 115–19.
9. Jenkinson LR, Norris TL, Watson A. Dietary guidelines for ambulatory pH recording. *Gut* 1986; **27**: 594–5.
10. Johnson LF, DeMeester TR. Twenty-four hour pH monitoring of the distal esophagus; a quantitative measure of gastro-oesophageal reflux. *Am J Gastroenterol* 1974; **62**: 325–32.
11. Washer GF, Gear MWL, Dowling BL *et al*. Randomised prospective trial of Roux-en-Y duodenal diversion *versus*

fundoplication for severe reflux oesophagitis. *Br J Surg* 1984; **71**: 181–4.

12. Gear MWL, Gillison EW, Dowling BL *et al.* Randomised prospective trial of the Angelchik anti-reflux prosthesis. *Br J Surg* 1984; 71: 681–3.
13. DeMeester TR, Johnson LF, Kent AH. Evaluation of current operations for the prevention of gastro-oesophageal reflux. *Ann Surg* 1974; **180**: 511–22.
14. Dedinsky GK, Vane DW, Black CT *et al.* Complications and re-operation afer Nissen fundoplication in childhood. *Am J Surg* 1987; **153**: 177–82.
15. Donahue PE, Bombeck CT. The modified Nissen fundoplication – reflux prevention with gas bloat. *Chir Gastroent* 1977; **11**: 15–27.
16. Negre JB. Post fundoplication syndromes. Do they restrict the success of Nissen fundoplication? *Ann Surg* 1983; **198**: 698–700.
17. Durrans D, Armstrong CP, Taylor TV. The Angelchik anti-reflux prosthesis – some reservations. *Br J Surg* 1985; **72**: 525–7.
18. Wale RJ, Royston CMS, Bennett JR *et al.* Prospective study of the Angelchik anti-reflux prosthesis. *Br J Surg* 1985; **72**: 520–5.
19. Fisher RS, Malmud LS, Lobis IF *et al.* Anti-reflux surgery for symptomatic gastro-esophageal reflux – mechanism of action. *Dig Dis* 1978; **23**: 152–60.
20. Jamieson GG. Anti-reflux operations: how do they work? *Br J Surg* 1987; **74**: 155–6.
21. Hope CE, Micyer GW, Castell DO. Is measurement of lower esophageal sphincter pressure clinically useful? *Dig Dis Sci* 1981; **26**: 1025–30.
22. Higgs RH, Castell DO, Farrell RL. Evaluation of the effect of fundoplication on the incompetent lower esophageal sphincter. *Surg Gynecol Obstet* 1975; **141**: 571–5.
23. Bombeck CT, Coeltro RGP, Nyhus LM. Prevention of gastro-esophageal reflux after resection of the lower esophagus. *Surg Gynecol Obstet* 1970; **136**: 1035–43.
24. Butterfield WC. Current hiatal hernia repairs. Similarities, mechanisms and extended indications – an autopsy study. *Surgery* 1971; **69**: 910–16.
25. O'Sullivan GC, DeMeester TR, Joelsson BE *et al.* Interaction of lower esophageal sphincter pressure and length of sphincter in the abdomen as determinants of gastro-esophageal competence. *Am J Surg* 1982; **143**: 40–7.
26. Clark J, Cuschieri A. Evidence for the flutter valve mechanism of gastro-oesophageal competence. *Br J Surg* 1980; **67**: 599–603.
27. Samelson SL, Weiser HF, Bombeck CT. A new concept in the surgical treatment of gastro-esophageal reflux. *Ann Surg* 1983; **197**: 254–9.
28. Skinner DB. Pathophysiology of gastro-oesophageal reflux. *Ann Surg* 1985; **202**: 546–56.
29. Watson A. A clinical study of the role of anti-reflux surgery combined with endoscopic dilatation in peptic esophageal stricture. *Am J Surg* 1984; **148**: 346–9.
30. Barlow AP, Norris TL, Watson A. Does healing of oesophagitis depend solely on reducing oesophageal acid exposure? *Gut* 1989; **30**: A1490.

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Surgery improves defective oesophageal peristalsis in patients with gastro-oesophageal reflux

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Postoperative manometry was carried out in 12 patients with gastro-oesophageal reflux associated with hypomotility of the oesophageal body. A Nissen fundoplication was carried out in all patients. After a median follow-up of 3·5 years, patients underwent clinical, endoscopic, radiological, manometric and pH-metric evaluation. Manometric results revealed an overall improvement in oesophageal motor function with an increase in the amplitude of deglutition waves and a decrease in the percentage of deglutitions without response. Six of the patients (one with complete motor failure) recovered normal peristaltic function. Non-specific oesophageal motor disorders may be secondary to gastro-oesophageal reflux and are reversible in nature.

Gastro-oesophageal reflux is frequently associated with motor disorders of the oesophageal body[1–10]. This alteration may be characterized by a pattern of hypermotility or motor incoordination, which at times constitutes diffuse oesophageal spasm[1,3,11]. Gastro-oesophageal reflux is more frequently linked with a hypokinetic pattern, defined as the occurrence of either hypotensive peristalsis or failed primary peristalsis in the distal oesophagus for more than half the deglutitions, mimicking in some cases the aperistalsis of scleroderma[1,2,5,9,12]. Such dysfunction seems to increase with the severity of the oesophagitis.

Some[1–3,9,12–15] claim that this peristaltic dysfunction is secondary to reflux, while others[10,16–18] consider that it is a primary alteration which precedes and contributes to severe forms of reflux injury.

The aim of this study was to examine the results obtained following surgical treatment in a group of patients with reflux oesophagitis associated with hypomotility of the oesophageal body.

Patients and methods

One hundred and twenty patients underwent a Nissen fundoplication for gastro-oesophageal reflux between 1978 and 1986. Twenty-six (not selected) received preoperative and postoperative manometry. The rest underwent just one of the manometric studies (preoperative or postoperative) or rejected both. Of these 26 patients, 12 demonstrated hypomotility of the oesophageal body and were the subjects of this study. The other 14 presented normal motility (eight patients) or hyperkinesia of the oesophageal body (six patients) and were therefore excluded. The diagnosis of hypomotility was established on the basis of the following manometric criteria: more than 30 per cent of deglutitions without response and/or appearance of low amplitude deglutition waves (less than 20 mmHg) in over 50 per cent of deglutitions, waves which were often simultaneous. The surgical procedure consisted of a 360° fundoplication around a 48–50 Fr mercury bougie, in no case longer than 3 cm.

There were seven men and five women, with a median age of 48·5 years (range 33–63 years). Clinical history ranged from 3 months to 30 years with a median of 4·5 years. Symptomatology is shown in *Table 1*. No patient had scleroderma or previous surgery of the cardia. All patients had a small hiatus hernia on radiology. Endoscopy revealed grade I oesophagitis in three patients, grade II in one, grade III in four and grade IV (Barrett's) in the remaining four (Savary–Miller's classification[19]). None had evidence of oesophageal stricture. The patients underwent 24-h pH monitoring which revealed pathological acid reflux in all, with a median percentage of total time with $pH < 4$ of 12 per cent (range 5·7–34·3 per cent) (Johnson and De Meester criteria[20]). Severe and persistent symptoms of reflux disease after 6 months of appropriate medical treatment led to surgery. Oesophageal intraluminal manometry was performed on the 12 patients and on a control group of 20 healthy volunteers (ten men and ten women) with a median age of 43 years (range 20–65 years), using a probe with three microtransducers (Gaeltec Ltd. Microtransducers Pressure, Dunvegan, UK) located at the distal end 120° radially to one another and spaced 5 cm apart, and a Hewlett-Packard 7754 B System polygraph (Palo Alto, California, USA). The method has been described previously[21]. The parameters studied were total length (cm); abdominal length (cm) and basal pressure (mmHg) of the lower oesophageal sphincter; amplitude of the contractile waves of the distal third of the oesophageal body (mmHg); the percentages of tertiary waves and of deglutitions without response in the distal third of the oesophageal body.

After a median follow-up of 3·5 years (range 1–10 years), the patients underwent clinical, radiological, endoscopic, manometric and pH-metric evaluation. Clinical assessment, performed annually, was by Visick grading. Postoperative oesophageal intraluminal manometry and 24-h pH monitoring were performed on the same day after a median follow-up of 2 years (range 1–9 years). Results were compared with preoperative data and values of the control group.

Results are expressed as median (range), and statistical evaluation of the differences between the groups was by the Wilcoxon rank sum test for the analysis of non-parametric data. The possible correlations between the type of oesophageal body response to Nissen fundoplication and different factors such as the length of history (less than 5 years *versus* greater than 5 years), grade of preoperative oesophagitis (grades I and II *versus* grades III and IV), and the time interval between the Nissen fundoplication and the manometric study (less than 3 years *versus* more than 3 years) were studied using χ^2 with Yates' correction.

All subjects gave fully informed consent and the investigation methods were approved by the Ethical Committee of the Virgen de la Arrixaca Hospital.

Results

Eleven patients were free of symptoms (Visick I); the remaining patient had occasional dysphagia (Visick II). Radiological studies showed no hiatus hernia, and postoperative endoscopy

Table 1 *Preoperative symptoms*

Symptom	Number
Heartburn	12 (100)
Regurgitation	6 (50)
Dysphagia	4 (33)
Episodes of pulmonary aspiration	3 (25)
Chest pain	2 (17)
Upper gastrointestinal bleeding	1 (8)

Values in parentheses are percentages

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Table 2 *Manometric evaluation of the lower oesophageal sphincter and the distal third of the oesophageal body*

	Postoperative group ($n=12$)	Preoperative group ($n=12$)	Control group ($n=20$)
Overall length of LOS (cm)	4·2 (3–6)	3 (2–4·5)*	4·2 (2–4·5)‡
Abdominal length of LOS (cm)	3 (2–5·5)	0·7 (0–1·5)‡	1·9 (1·5–3)‡
Basal pressure of LOS (mmHg)	14·9 (6–29)	5 (2–9·6)†	16 (8·5–35·1)
Amplitude of the contractile waves (mmHg)	27·5 (12–57)	14·6 (0–35)*	27·1 (21–42)
Percentage of deglutitions without motor response	8 (0–53)	50 (30–100)†	0 ‡
Percentage of tertiary waves	29·2 (0–100)	33 (0–100)	0 (0–25)

Values are median (range). * $P<0{\cdot}05$, † $P<0{\cdot}01$, ‡ $P<0{\cdot}001$ compared with postoperative group. LOS, lower oesophageal sphincter

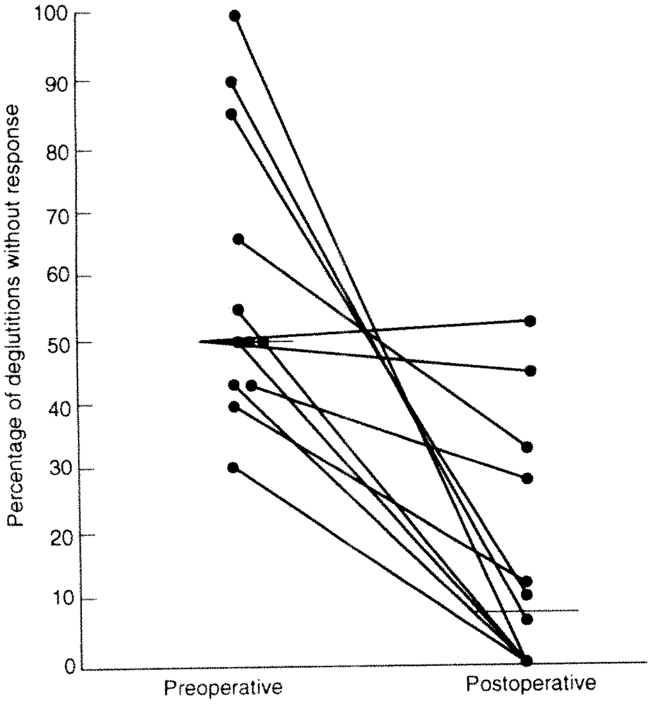

Figure 1 *Preoperative and postoperative percentage of deglutitions without response. Bars show median values*

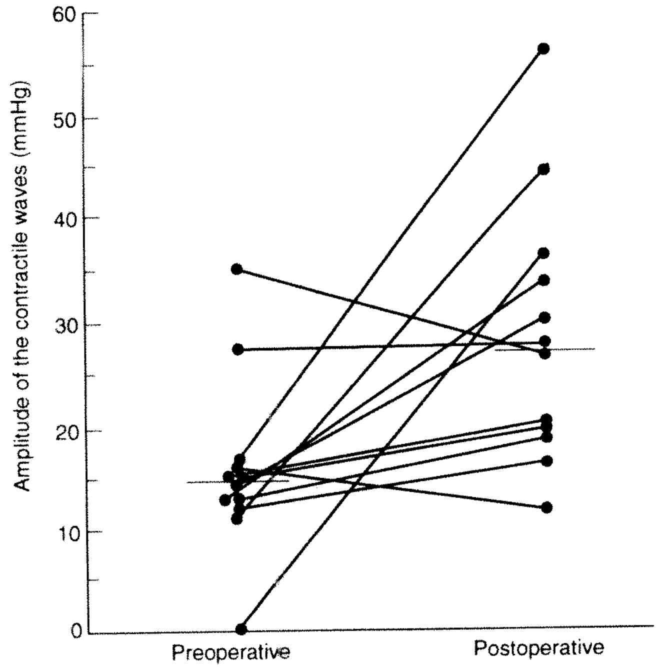

Figure 2 *Preoperative and postoperative amplitude of the contractile waves. Bars show median values*

showed resolution of inflammatory signs in the distal oesophagus in all patients except the four with Barrett's change, which showed no resolution. Monitoring of pH revealed no abnormal acid reflux in any patient, with a median percentage of total time with pH < 4 of 0·5 per cent (range 0–1·9 per cent), similar to the control group (median 0·8 per cent, range 0–2·2).

Postoperative oesophageal intraluminal manometry (*Table 2*) showed that Nissen fundoplication significantly increases the basal pressure of the lower oesophageal sphincter, and its total and infradiaphragmatic length. In the oesophageal body, Nissen fundoplication produces a significant decrease in the percentage of deglutitions without response and a significant increase in the amplitude of contractions. The percentage of tertiary waves is not significantly altered. Analysing results case by case (*Figures 1* and *2*), nine of the 12 patients, one with complete akinesia, showed obvious improvement in motor function (normal in six). In two patients, the motor pattern remained the same. In the patient with occasional dysphagia the preoperative motor disturbance became more abnormal, with an increase in the percentage of tertiary waves. There was no correlation between the recovery of peristalsis and the factors mentioned above.

Discussion

In 1965, Olsen and Schlegel first demonstrated an association between gastro-oesophageal reflux and different forms of defective oesophageal body peristalsis[1]. They described two hypomotility patterns which they defined as weak contractions and complete motor failure, and considered these secondary to reflux, parallel to the intensity of oesophagitis and irreversible in nature. They claimed that surgical treatment for gastro-oesophageal reflux should be carried out before motor abnormalities appear as the surgical repair might exacerbate poor oesophageal emptying.

Some[2,3,9,12–15] believe that these disorders are secondary to gastro-oesophageal reflux and may even revert after healing of the oesophageal lesion. Others[4,10,16–18] find no significant improvement in oesophageal motor function after medical or surgical treatment and believe dysmotility to be a primary event in the multifactorial aetiology of reflux. Joelsson *et al.*[5] considered that surgery in patients with defective peristalsis may give unsatisfactory results, defining these cases as high risk. They suggest that repair of a large hiatus hernia could improve the motor function of the distal oesophagus since a large hernia may alter the distal oesophageal motor 'pump'.

This study reveals that surgical treatment for gastro-oesophageal reflux improves oesophageal motor function in over 50 per cent of patients, suggesting its secondary and reversible nature. We, like others[3,12,14,22], favour surgical treatment for gastro-oesophageal reflux in patients who are refractory to medical treatment, irrespective of preoperative manometric findings.

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References

1. Olsen AM, Schlegel JF. Motility disturbances caused by esophagitis. *J Thorac Cardiovasc Surg* 1965; **50**: 607–12.
2. Atkinson M. The oesophago-gastric junction. In: Badenoch J, Brooke BB, eds. *Recent Advances in Gastroenterology*. London: Churchill Livingstone, 1965; 49–67.
3. Affolter H. Pressure characteristics of reflux esophagitis. *Helv Med Acta* 1966; **5**: 395–402.
4. Russell COH, Pope CHE, Gannan RM, Allen FD, Velasco N, Hill LD. Does surgery correct esophageal motor dysfunction in gastroesophageal reflux? *Ann Surg* 1981; **194**: 290–6.
5. Joelsson BE, De Meester TR, Skinner DB, Lafontaine E, Waters PF, O'Sullivan GC. The role of the esophageal body in the antireflux mechanism. *Surgery* 1982; **92**: 417–24.
6. Stanciu C, Bennett JR. Oesophageal acid clearing: one factor in the production of reflux oesophagitis. *Gut* 1974; **15**: 852–7.
7. Siegel CI, Hendrix TR. Esophageal motor abnormalities induced by acid perfusion in patients with heartburn. *J Clin Invest* 1963; **42**: 686–95.
8. Corazziari E, Bontempo I, Anzini F *et al.* Motor activity of the distal oesophagus and gastro-oesophageal reflux. *Gut* 1984; **25**: 7–13.
9. Kahrilas PJ, Dodds WJ, Hogan WJ, Kern M, Arndorfer RC, Reece A. Esophageal peristaltic dysfunction in peptic esophagitis. *Gastroenterology* 1986; **91**: 897–904.
10. Katz PQ, Knuff TE, Benjamin SD, Castell DO. Abnormal esophageal pressures in reflux esophagitis: cause or effect? *Am J Gastroenterol* 1986; **81**: 744–6.
11. Bancewicz J, Osugi H, Marples M. Clinical implications of abnormal oesophageal motility. *Br J Surg* 1987; **74**: 416–19.
12. Moses FM. Reversible aperistalsis as a complication of gastro-esophageal reflux disease. *Am J Gastroenterol* 1987; **82**: 272–5.
13. Marshall JB, Gerhardt DC. Improvement in esophageal motor dysfunction with treatment of reflux esophagitis. A report of two cases. *Am J Gastroenterol* 1982; **77**: 351–4.
14. Gill RC, Bowes KL, Murphy PD, Kingma J. Esophageal motor abnormalities in gastro-esophageal reflux and the effects of fundoplication. *Gastroenterology* 1986; **91**: 364–9.
15. Shirazi S, Schulze-Delrieu K, Custer-Hagen T, Brown CK, Ren J. Motility changes in opossum esophagus from experimental esophagitis. *Dig Dis Sci* 1989; **34**: 1668–76.
16. Eriksen CA, Sadek SA, Sutton D *et al.* Reflux oesophagitis and oesophageal transit: evidence for a primary oesophageal motor disorder. *Gut* 1988; **29**: 448–52.
17. Baldi F, Ferrarini F, Conganesi AM *et al.* Oesophageal function before, during and after healing of erosive oesophagitis. *Gut* 1988; **29**: 157–60.
18. Battle WS, Nyhus LH, Bombeck CT. Gastro-esophageal reflux: diagnosis and treatment. *Ann Surg* 1973; **177**: 560–5.
19. Savary M, Miller G. *The Esophagus. Handbook and Atlas of Endoscopy*. Switzerland: Gassmann AG, 1978; 135–9.
20. Johnson LF, De Meester TR. Twenty-four hour monitoring of the distal esophagus. A quantitative measure of gastro-esophageal reflux. *Am J Gastroenterol* 1974; **62**: 325–32.
21. Parrilla P, Ortiz A, Martinez de Haro LF, Aguayo JL, Ramirez P. Evaluation of the magnitude of gastro-oesophageal reflux in Barrett's oesophagus. *Gut* 1990; **31**: 964–7.
22. Mughal MM, Bancewicz J, Marples M. Oesophageal manometry and pH recording does not predict the bad results of Nissen fundoplication. *Br J Surg* 1990; **77**: 43–5.

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Injection sclerotherapy for bleeding varices: risk factors and complications

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Risk factors for complications after injection sclerotherapy were studied in 163 patients undergoing 667 treatments for bleeding oesophageal varices. The overall mortality rate was 7 per cent per injection sclerotherapy session; 16 per cent per acute session and 2·4 per cent per elective session. Acute variceal bleeding was controlled by injection sclerotherapy in 91 per cent of patients. Complications occurred after 16 per cent of injection sclerotherapy sessions. Deaths and complications were significantly associated with poor modified Child's grading (P<0·001), the first variceal bleed (P<0·001), acute injection sclerotherapy (P<0·001) and the use of the rigid oesophagoscope (P<0·001).

Injection sclerotherapy is a well established treatment for bleeding oesophageal varices. There is some evidence that sclerotherapy reduces the number of bleeding episodes[1,2] and may improve survival[3,4]. There is continuing debate about the most appropriate techniques of treatment, and the optimal time interval between treatments is not known. Different endoscopes[5], sclerosants[6] and injection techniques have been employed. Over a period of 8 years, injection sclerotherapy was the principal method of treatment for oesophageal varices in the University Department of Surgery, Glasgow. The patients treated have been reviewed to establish the safety and efficacy of the procedure, attempting to identify risk factors for complications.

Patients and methods

Patients with bleeding oesophageal varices treated by injection sclerotherapy in the University Department of Surgery, Glasgow Royal Infirmary between 1 January 1979 and 31 December 1986 were identified.

Patients presenting with acute variceal haemorrhage were treated initially by resuscitation and oesophageal tamponade if necessary. Sclerotherapy was undertaken when the patient was haemodynamically stable and was the principal means of preventing recurrent variceal bleeding. Patients who were less than 50 years old, who were in modified Child's group A (Reference 7) and who did not have alcoholic liver disease were considered for portacaval shunt. Up to 31 December 1985 oesophageal transection was reserved for patients in whom sclerotherapy had failed to prevent recurrent bleeding. During 1986 five patients in modified Child's grades A and B were entered into a multicentre trial comparing oesophageal transection with sclerotherapy.

All patients were treated by repeat injection sclerotherapy at time intervals determined by the endoscopist. Sclerotherapy was usually performed monthly until a significant reduction in the size of the varices was achieved. If further gastrointestinal bleeding occurred endoscopy was repeated to establish the source of bleeding and sclerotherapy performed if oesophageal varices were thought to be responsible. In the early years under review a rigid Negus oesophagoscope with a Robert's needle was used with the patient under general anaesthesia. Since 1984 injection has been performed, whenever possible, using a fibreoptic endoscope (Olympus GIF-1T or GIF-XQ, Keymed, Southend, UK) and a flexible needle (Olympus NM3, Keymed) under sedation with diazepam (Diazemuls® 5–30 mg intravenous, Kabivitrum Ltd., Uxbridge, UK). All injections were performed intravariceally using aliquots of 1–2 ml ethanolamine oleate to a maximum of 20 ml per session.

Details regarding presentation, previous treatment and aetiology of portal hypertension were documented. Liver function at presentation and at each sclerotherapy session was recorded in the form of a modified Child's grading[7]. The timing of sclerotherapy relative to the variceal bleed was recorded. Most patients underwent sclerotherapy within 48 h of any bleed. Acute sclerotherapy was defined as that which was undertaken within 7 days of a bleed. The type of endoscope used and the size of the varices in terms of protrusion into the lumen of the oesophagus (large, moderate, small, obliterated) were noted. Evidence of complications of previous injection sclerotherapy such as ulceration or stricture requiring dilatation was recorded.

Early complications of injection sclerotherapy were recorded. Post-injection bleeding was defined as blood loss at or within 24 h of injection[8] which required blood transfusion (fall in haemoglobin level to <100 g/l or shock due to bleeding with systolic blood pressure <100 mmHg or pulse rate >100). Bleeding from varices more than 24 h after sclerotherapy was recorded as a failure. Chest infection was diagnosed if there was clinical or radiological evidence of chest infection requiring antibiotic therapy. Clinical suspicions of oesophageal perforation were confirmed by Gastrografin® (Schering AG, Berlin, Germany) swallow. Late complications included oesophageal ulceration and stricture seen at subsequent endoscopy or presenting with symptoms before the next endoscopy session. Mortality was recorded as death during the admission on which sclerotherapy had been undertaken. Cause of death was noted. Deaths 'related to sclerotherapy' included oesophageal perforation or post-injection bleeding and those which might have been related to sclerotherapy such as due to chest infection after sclerotherapy. Deaths secondary to liver failure were not recorded as related to sclerotherapy.

Comparisons of the statistical data were performed using χ^2 tests and Fisher's exact test as appropriate.

Results

Between 1 January 1979 and 31 December 1986, 209 patients with oesophageal varices were referred and 164 patients underwent injection sclerotherapy. Of the remaining 45 patients, nine had not bled from their varices, 23 died during or after resuscitation, eight were treated by oesophageal transection and four by portacaval shunt. One patient discharged himself against medical advice and had no further treatment. The case notes of one patient could not be traced, so 163 patients were studied and their details are shown in *Tables 1* and *2*. The 163 patients had a total of 667 sessions of injection sclerotherapy.

The overall mortality rate was 7 per cent per injection sclerotherapy session, with a rate of 16 per cent per acute session and 2·4 per cent per elective session (*Table 3*). Of the 219 acute injection sclerotherapy sessions, 160 were performed within 72 h of an acute bleed and 20 patients had further variceal bleeding during that admission. One patient had bleeding due to gastritis; 11 patients bled from oesophageal ulceration after sclerotherapy but nine of these patients had been discharged and were readmitted with the subsequent bleed. One death was attributed to elective sclerotherapy in a patient with modified

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Child's grade C with post-injection bleeding 2 weeks after a variceal bleed requiring urgent oesophageal transection. The patient died from liver failure 6 days later. In all, 563 (84 per cent) of the 667 sclerotherapy sessions were uncomplicated.

Table 4 shows the incidence of specific complications. Chest infection was more common in patients with modified Child's grade C, after rigid oesophagoscopy and after an acute variceal bleed. Post-injection bleeding was more common in poor-risk patients with recent variceal bleeding. Two of the 39 patients who had post-injection bleeding required oesophageal transection for its control. Post-injection bleeding was associated with the presence of large varices; only two post-injection bleeds occurred in patients with small varices compared with 37 episodes in patients with moderate or large varices.

Table 1 *Details of previous treatment of 163 patients with bleeding oesophageal varices subsequently treated by injection sclerotherapy*

Previous treatment	No. of patients
None	134
Sclerotherapy elsewhere	14
Oesophageal transection	1
Portacaval shunt	2
Propranolol	6
Splenectomy	3
Ligation or oversewing of varices	3

Table 2 *Characteristics of 163 patients with bleeding oesophageal varices treated by injection sclerotherapy*

Age at presentation, mean(s.d.) (years)	54·6(13·8)
Sex ratio (male:female)	2:1
Aetiology of portal hypertension	
Alcohol	92
Primary biliary cirrhosis	10
Chronic active hepatitis	19
Cryptogenic cirrhosis	8
Portal vein thrombosis	7
Congenital hepatic fibrosis	2
Other	14
Not known	11
Modified Child's grade at presentation	
A	22
B	65
C	76

All eight oesophageal perforations occurred after rigid oesophagoscopy and seven of these within 7 days of the first variceal bleed. Six of these eight patients died. The two survivors were both in modified Child's grade B and were treated non-operatively. Five patients who died were treated similarly. Two improved and the oesophageal leak sealed but they deteriorated and died from liver failure. One patient treated by oesophagectomy after a leak at 10 days post-sclerotherapy died after surgery and was found to have a small squamous carcinoma at the site of the leak.

All 15 patients who developed oesophageal ulceration received 15 ml or more of sclerosant at one session. Thirteen of 15 ulcers occurred after acute injection sclerotherapy and 11 presented with recurrent bleeding. Four ulcers were asymptomatic and were detected at subsequent elective endoscopy.

Eight patients developed oesophageal strictures requiring dilatation and all but one had had at least five injection sclerotherapy sessions before the stricture occurred. The eighth patient developed a stricture after an oesophageal perforation. No patient required more than three oesophageal dilatations.

To estimate whether rigid oesophagoscopy influenced the complication rates, a high-risk group of patients undergoing endoscopy – those performed within 7 days of the first variceal bleed – was examined (*Figure 1*). Although the modified Child's grading of the patients in the groups was not significantly different (Fisher's exact test $P>0{\cdot}5$), there was a significantly increased risk of complication associated with the use of the rigid oesophagoscope (χ^2 test $P<0{\cdot}05$). The risk of post-injection bleeding, previously reported to be increased due to technical difficulties and poor view with the fibreoptic endoscope[9], was not reduced in the group treated with acute injection sclerotherapy using the rigid endoscope.

Discussion

In this study a high complication rate was observed in a relatively poor-risk group of patients (56 per cent alcoholic; 47 per cent Child's C grade at presentation; 33 per cent injection sclerotherapy within 7 days of a variceal bleed). The overall admission mortality rate of 7 per cent per injection sclerotherapy session (16 per cent acute; 2·4 per cent elective) compares with mortality rates of 14·9 per cent per acute session in the study of Spence and colleagues[1] and 6·1 per cent in the study of Soderlund and Ihre[10] for combined acute and elective sclerotherapy. A 2·4 per cent admission mortality rate for

Table 3 *Number of uncomplicated sclerotherapy sessions, admission mortality and mortality related to sclerotherapy during 667 admissions for injection sclerotherapy in 163 patients*

	Sclerotherapy sessions	Uncomplicated sclerotherapy sessions	Deaths during admission	Deaths related to sclerotherapy
Modified Child's grade				
A	136	130 (96)	0	0
B	267	230 (86)	10	4
C	264	203 (77)	36	20
Age in years				
<40	91	85 (93)	2	1
41–50	136	121 (89)	6	3
51–60	224	178 (79)	22	11
61–70	162	135 (83)	9	6
>70	54	44 (81)	7	3
First bleed	156	103 (66)	25	17
Other	511	460 (90)	21	7
Acute sclerotherapy	219	136 (62)	35 (16)	23
Elective sclerotherapy	448	427 (95)	11 (2·4)	1
Rigid oesophagoscope	138	78 (57)	22	18
Fibreoptic endoscope	529	485 (92)	24	6

Values in parentheses are percentages. Risk of complication or death was significantly increased in modified Child's grade C ($P<0{\cdot}001$), first variceal bleed ($P<0{\cdot}001$), injection sclerotherapy within 7 days of variceal bleeding ($P<0{\cdot}001$) and when sclerotherapy was performed using the rigid oesophagoscope ($P<0{\cdot}001$); χ^2 tests used to compare groups except for deaths *versus* Child's C or A/B (Fisher's exact test)

Table 4 *Details of complications after 667 injection sclerotherapy sessions in relation to age, modified Child's grading, timing and method of sclerotherapy. All figures relate to number of episodes*

	Injection sclerotherapy sessions	Chest infection	Post-injection bleeding	Oesophageal perforation	Oesophageal ulcer	Other
Modified Child's grade						
A	136	1	4	0	1	1
B	267	11	13	3	9	2
C	264	27	22	5	5	4
First bleed	156	23	16	7	7	1
Other	511	16	23	1	8	6
Acute sclerotherapy	219	35	28	7	13	4
Elective sclerotherapy	448	4	11	1	2	3
Rigid oesophagoscope	138	27	15	8	10	2
Fibreoptic endoscope	529	12	24	0	5	5
Total	667	39	39	8	15	7

Four patients sustained more than one complication. The complications classified as 'other' comprised one deep venous thrombosis, five allergic reactions after sclerotherapy (four in one patient) and one severe episode of delirium tremens

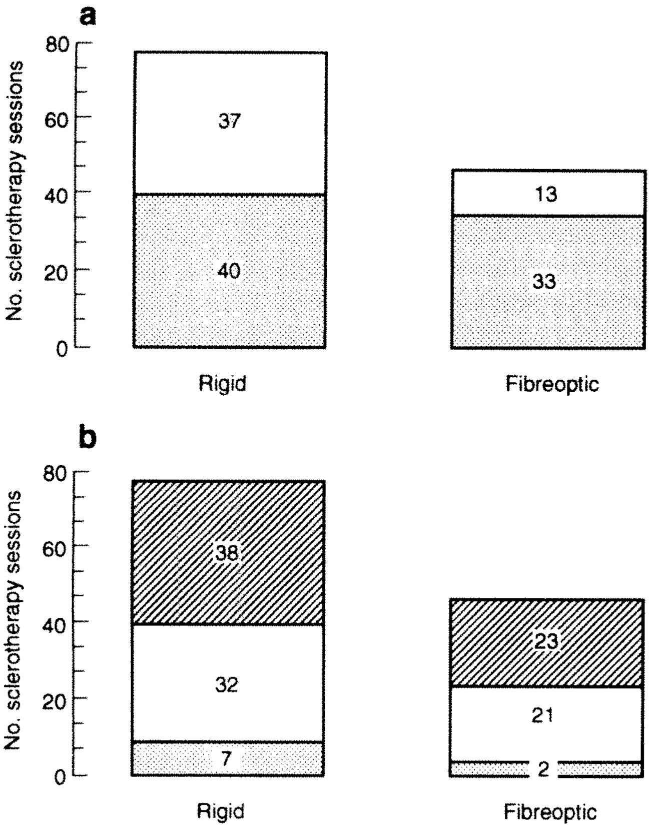

Figure 1 **a** *Comparison of complicated* (□) *and uncomplicated* (□) *and* **b** *comparison of modified Child's grades* (▨, *C;* □, *B;* □, *A*) *in the high-risk group of patients who underwent injection sclerotherapy within 7 days of their variceal bleed in the rigid and fibreoptic endoscopy groups; Fisher's exact test was used to compare the numbers in the modified Child's grades and* χ^2 *tests to compare the risk of complication in the groups*

elective injection sclerotherapy seems high in comparison with some studies[11] but compares with the Belfast group's recent report of four 'early deaths' after 221 elective injections[5]. Ten deaths due to liver failure (with only one death attributable to injection sclerotherapy itself) were included and it might be argued that these end-stage patients should not have undergone sclerotherapy.

Poor outcome in variceal haemorrhage is known to be associated with poor liver function[12] and is more likely after the first bleed[13]. The increased risk of complication or death after sclerotherapy in these groups is therefore not surprising. Injection sclerotherapy soon after variceal haemorrhage has previously been reported to have a higher complication rate[9]. Rigid oesophagoscopy appears to be associated with an increased risk of complications, partly due to oesophageal perforation but perhaps also to the general anaesthetic necessary for the procedure. The previously reported reduction in post-injection bleeding[9] was not seen. This may be due to increasing experience with fibreoptic endoscopy over a number of years.

Age has little influence on mortality or complications after sclerotherapy[14] and, in the presence of good liver function, aggressive treatment of oesophageal varices in the elderly is certainly justified.

Particular complications were found to be associated with different risk factors. Chest infections were associated with poor liver function, perhaps because encephalopathy increases the risk of aspiration. Aspiration is probably the main cause of the increased incidence of chest infection in the acute sclerotherapy group and general anaesthesia may increase the risk in the rigid oesophagoscopy group. Depressed reticuloendothelial system activity in patients with severe liver disease may play a role[15].

Bleeding after injection sclerotherapy may be due to the sclerotherapy or to recurrent variceal bleeding. Post-injection bleeding was arbitrarily defined as that occurring within 24 h of injection. This is more common in patients with poor liver function who have coagulation abnormalities. The data confirm[9] that bleeding is more common if sclerotherapy is performed soon after a variceal bleed.

All of the oesophageal perforations in this series occurred after rigid oesophagoscopy. The single suspected perforation occurring in an 'elective' patient took place after sclerotherapy performed 12 days after the first variceal bleed in a modified Child's C grade patient.

It is well known that the reported incidence of oesophageal ulceration as a complication of sclerotherapy depends on the frequency with which endoscopy is performed[16]. It is likely that a number of other patients in this series had asymptomatic oesophageal ulceration. The bleeding rate of 1·6 per cent per sclerotherapy session due to ulceration is similar to that reported by others[3].

The aim of any medical audit is to improve the results of treatment. Risk factors such as poor liver function are difficult to change. Sclerotherapy soon after variceal bleeding may carry an increased risk but early treatment is necessary to reduce the risk of early rebleeding with its high mortality rate[13]. Injection sclerotherapy by means of the rigid oesophagoscope does not appear to confer any advantage over sclerotherapy performed with the fibreoptic endoscope and the high complication rate would indicate that its use may contribute to the overall mortality rate.

References

1. Spence RAJ, Anderson JR, Johnston GW. Twenty five years of injection sclerotherapy for bleeding varices. *Br J Surg* 1985; **72**: 195–8.
2. Terblanche J, Kahn D, Campbell JAH *et al.* Failure of repeated injection sclerotherapy to improve long-term survival after oesophageal variceal bleeding. *Lancet* 1983; **ii**: 1328–32.
3. Macdougall BRD, Westaby D, Theodossi A, Dawson JL, Williams R. Increased long-term survival in variceal haemorrhage using injection sclerotherapy. Results of a controlled trial. *Lancet* 1982; **i**: 124–7.
4. The Copenhagen esophageal varices sclerotherapy project. Sclerotherapy after first variceal haemorrhage in cirrhosis. *N Engl J Med* 1984; **311**: 1594–1600.
5. Wilson RH, Campbell WJ, Spencer A, Johnston GW. Rigid endoscopy under general anaesthesia is safe for chronic injection sclerotherapy. *Br J Surg* 1989; **76**: 719–21.
6. Kitano S, Hashizume M, Yamaga H, Wada H, Iso Y, Iwanaga T, Sugimachi K. Human thrombin plus 5 per cent ethanolamine oleate injected to sclerose oesophageal varices: a prospective randomized trial. *Br J Surg* 1989; **76**: 715–18.
7. Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; **60**: 646–9.
8. Westaby D, Macdougall BRD, Melia W, Theodossi A, Williams R. A prospective randomised study of two sclerotherapy techniques for oesophageal varices. *Hepatology* 1983; **3**: 681–4.
9. Terblanche J. Sclerotherapy for emergency variceal haemorrhage. *World J Surg* 1984; **8**: 653–9.
10. Soderlund C, Ihre T. Endoscopic sclerotherapy v. conservative management of bleeding oesophageal varices. *Acta Chir Scand* 1985; **151**: 449–56.
11. Lai ECS, Choi TK, Fok M, Wong J. Injection sclerotherapy of oesophageal varices with the free-hand technique; experience in Hong Kong. *Br J Surg* 1986; **73**: 193–5.
12. Hislop IG, Waters TE, Kellock TD, Swynnerton B. The natural history of haemorrhage from oesophageal varices. *Lancet* 1966; **i**: 152–3.
13. Smith JL, Graham DY. Variceal haemorrhage. A critical evaluation of survival analysis. *Gastroenterology* 1982; **82**: 968–73.
14. Hoskings SW, Bird NC, Johnson AG, Triger DR. Management of bleeding varices in the elderly. *Br Med J* 1989; **i**: 152–3.
15. Rimola A, Soto R, Bory F, Arroyo V, Piera C, Rodes J. Reticuloendothelial system phagocytic activity in cirrhosis and its relation to bacterial infections and prognosis. *Hepatology* 1984; **4**: 53–8.
16. Westaby D, Melia WM, Macdougall BRD, Hegarty JE, Williams R. Injection sclerotherapy for oesophageal varices: a prospective randomised trial of different treatment schedules. *Gut* 1984; **25**: 129–32.

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Penetrating missile injuries in the Gulf war 1991

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During the recent Gulf war 63 patients with penetrating missile injuries (including 29 Iraqi prisoners of war) underwent operation in a British Army Field Hospital. Their injuries and initial operative management are reported. Fifty-one casualties (81 per cent) suffered an average of nine wounds (range 1–45) due to fragmentation weapons, and 12 casualties sustained bullet wounds. All wounds were explored following the established principles of war surgery. The extremities were involved in 48 patients (76 per cent). Eight compound long bone fractures were managed with external skeletal fixators applied at the time of initial operation. Laparotomy was performed on seven patients, one of whom died. The average duration of operation was 77 min for shrapnel wounds and 85 min for bullet wounds.

The recent Gulf conflict represented an unparalleled military success in the sphere of conventional warfare. The effectiveness of massive air bombardments and subsequent rapid armoured thrusts resulted in a short, sharp, one-sided offensive with unexpectedly few Allied wounded. It had been predicted that on a future conventional battlefield the effectiveness of modern explosive munitions would produce high mortality from high energy transfer wounds and blast injury, and that most casualties reaching hospital would have multiple low energy wounds caused by modern anti-personnel fragmentation devices[1-3].

The 32 Field Hospital was deployed as the most forward British surgical facility in support of the ground offensive. It handled both British casualties and Iraqi prisoners of war. We report on the initial operative procedures in 63 casualties and discuss specific aspects of their surgical management.

Patients and results

32 Field Hospital

The hospital was established in its forward position on 20 January 1991. It comprised a reception/triage area, an eight-bay resuscitation department, a treatment area, an eight-table operating theatre, eight surgical teams and 200 beds in four wards. In addition, a pathology laboratory and a radiography facility were available.

Injured casualties received initial resuscitation and treatment at Regimental Aid Posts and Field Dressing Stations. Following helicopter evacuation to 32 Field Hospital, resuscitation was continued and appropriate radiographic studies were performed. Data on patients who underwent operation were recorded on proformas to include the date and time, cause and nature of injury, duration of operation, operative findings and surgical management. Patients were evacuated on the first postoperative day to military general hospitals in southern Saudi Arabia.

Presentation and management of injuries

Between 20 January and 6 March, 1053 patients were received by the hospital and 100 operations were performed. Sixty-three casualties sustained penetrating trauma because of missile injuries: 31 were British, 29 were Iraqi prisoners of war and three were Egyptian. The causes of the missile injuries are outlined in *Table 1*; fragmentation weapons caused 80 per cent of the injuries, and three of 12 bullet wounds were high energy transfer injuries. *Table 2* reflects the predominance of limb wounds in both fragment and bullet injuries (76 per cent), compared with chest wounds (12 per cent) and abdominal wounds (11 per cent).

Fragmentation weapons inflicted multiple low energy transfer wounds affecting more than one body area in 63 per cent of cases (*Table 3*). One patient had sustained wounds to all four limbs, buttocks and back. The mean number of fragment injuries per patient was nine (range 1–45).

The average time for a casualty to reach the hospital was 10·2 h for Allied casualties and 24·7 h for Iraqi prisoners of war (*Table 4*). The

Table 1 *Causes of missile injuries* (n = 63)

Fragment		
Not specified	40	
Mine	5	
Grenade	6	
Total		51 (80%)
Bullet		
9 mm	5	
7·62 mm	4	
5·56 mm	1	
Unknown	2	
Total		12 (20%)

Table 2 *Penetrating missile wounds: site of injury*

	Shrapnel (*n* = 51)		Bullet (*n* = 12)		Combined (*n* = 63)	
Site	No.	%	No.	%	No.	%
Head	4	8	0	0	4	6
Extremity	41	80	7	58	48	76
Upper limb	24	47	4	33	28	44
Lower limb	40	78	7	58	47	75
Chest	8	16	0	0	8	12
Abdomen	6	12	1	8	7	11
Buttocks	16	31	1	8	17	26
Back	4	8	0	0	4	6

Table 3 *Shrapnel wounds: number of body areas involved* (n = 51)

	Patients	
No. of areas	No.	%
1	19	37
2	10	20
3	10	20
4	9	17
≥5	3	6

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Table 4 *Mean time for Allied and Iraqi patients to reach hospital, operating theatre and duration of operation*

	No.	Time to reach hospital (h)	Preoperative period (h)	Duration of operation (min)
Allied troops	34	10·2	2·1	76·2
Iraqis	29	24·7	4·5	97·5

Table 5 *Type of injury and type of treatment for bullet and shrapnel wounds* (n = *63*)

Injury and treatment	Bullet (*n* = 12)	Shrapnel (*n* = 51)	Total (%) (*n* = 63)
Soft tissue	6	51	57 (85)
Wound excision	6	51	
Bone injury	6	17	23 (35)
External fixation	3	5	
Amputation	0	4	
POP splintage	3	8	
Thoracic injury	0	5	5 (7·5)
Chest drain	0	5	
Abdominal injury	1	6	7 (11)
Laparotomy	1	6	
Vascular injury	1	1	2 (3)
Vein patch		1	
Lateral suture	1		

POP, plaster of Paris

mean duration of operation was 78·7 min; it was longer for bullet wounds (84·6 min) than for fragment injuries (77·3 min). These times include both the induction of anaesthesia and extubation, which were performed on the table.

Soft tissue wounds. Most fragment wounds affected soft tissue only (*Table 5*). All soft tissue wounds were explored according to established principles of war surgery[4]. Wound edges were excised, permitting free access to the damaged tissues beneath. Limb incisions were longitudinal, facilitating decompression of underlying muscle and visualization of damaged structures within the wound cavity. Viability of muscle was determined by colour, texture, contractility and lack of bleeding. All non-viable muscle and fat was excised, and foreign bodies that were easily accessible were removed.

Wounds were irrigated with hydrogen peroxide and dressed with dry gauze. Benzylpenicillin had been administered to all casualties before arrival in hospital. Flucloxacillin was added to this regimen at operation, and both were continued for a minimum of 5 days.

Bone injury. Bone was fractured in six patients (50 per cent) with bullet wounds and 17 patients (33 per cent) with fragment wounds. Following wound excision and lavage, loose avascular splinters of bone were removed together with foreign bodies. External skeletal fixators (Centrafix, Military Pattern, Howmedica Ultra-X, New Jersey, USA) were applied to eight limbs at the initial operation as follows: humerus, two; ulna, one; tibia, four; and ankle and foot, one. All these fractures were either comminuted or associated with segmental bone loss. They were characterized by severe soft tissue injury requiring extensive surgical excision and wide fasciotomy. When applying the fixators, simple, unilateral, single-plane configurations were constructed. Pin tracts were pre-drilled, and pins were introduced by hand-drill through generous skin and fascia releasing incisions. When bone mass was lost, the fracture was held distracted to preserve limb length and axial alignment. Restoration of continuity was not practised in tendon and nerve injury.

Three patients underwent complete traumatic amputations (bilateral through-knee, Symes, and mid-forearm). Plaster of Paris splintage was applied in 11 hand and foot injuries.

Abdominal injury. Six patients with fragment wounds and one with a bullet wound received injuries to the abdomen necessitating laparotomy (*Table 6*). Fragment wounds to the liver did not cause serious bleeding, and no further procedure was required. Case 3 was the only fatality, the patient having sustained multiple fragment wounds to both lower limbs, buttocks and abdomen, with perforation of the liver, spleen and rectum.

Thoracic injury. Thoracic penetration resulted in haemopneumothorax in five patients with multiple fragment injuries. All were managed with local wound excision and chest drainage without the necessity for thoracotomy.

Vascular injury. Vascular injury was rare: one fragment wound to the brachial artery was reconstructed using a vein patch graft, and a bullet wound to the profunda femoris artery was repaired using a lateral suture technique.

Discussion

Despite the potential magnitude of the Gulf conflict, Allied casualty figures were low. The pattern of wounding seen in this small series was in keeping with experience from previous conventional battles[1,4,5]. Fragment wounds accounted for 81 per cent of casualties and were caused by modern anti-personnel weapons. An average of nine low energy transfer wounds were inflicted per patient. This figure emphasizes the inherent design features of the modern preformed fragment device, designed largely to incapacitate rather than to kill.

The average operating time of 77 min illustrates the burden that the treatment of non-life-threatening shrapnel-injured casualties can impose upon surgical resources during war. When faced with the circumstances of multiple wounds in multiple patients, the surgeon may be tempted to adopt less aggressive surgical management[6,7]. Our experience of battlefield injuries included many malnourished casualties with multiple fragment wounds, which were typically heavily contaminated and more than 24 h old. At operation, the extent and degree of tissue necrosis beneath the small puncture fragment wounds illustrated that, even at moderate range, these fragments generate sufficient energy transfer to form a temporary cavity, which results in skin and fibres of clothing being dispersed in radial fashion within the wound. These findings reinforce the military dictum that all penetrating missile wounds should be thoroughly explored and that one should err on the side of a more radical excision[7–9]. Of the 63 casualties, 48 (76 per cent) sustained limb wounds in this series. Missile fractures were seen in 23 of these 48 patients (48 per cent), but only eight (17 per cent) involved long bones and required external fixation. In the last two decades, external skeletal fixation has undergone a renaissance in the management of severe limb wounds associated with fractures in war[10,11]. This fact has been due in large part to improvements in design and the development of basic principles that govern their safe and effective application[12]. Experience in recent conflicts has emphasized that an ample supply of fixators is essential in war and that military surgeons should be trained in their use[11]. The external fixators used in our eight cases were simple, versatile and disposable systems specifically designed for use by surgeons in field hospitals.

Table 6 *Management of abdominal injuries*

Patient	Laparotomy findings	Operative procedure
1	Penetration of liver and common bile duct	T tube drainage of common bile duct, drainage of liver
2	Penetration of liver	No procedure
3*	Penetration of liver, spleen and rectum	Splenectomy, Hartmann's procedure
4	Penetration of stomach	Two-layer closure
5	Negative laparotomy	—
6	Penetration of liver	No procedure
7†	Penetration of rectum, ileum and caecum	Right hemicolectomy, ileostomy, mucus fistula and Hartmann's procedure

* Patient died; † gunshot wound

Coupland has suggested that application of an external fixator has a lower priority than wound excision and should be delayed until delayed wound closure[13]. We found that external fixators applied at the time of initial operation provided immediate stabilization of soft tissues and assured limb length and axial alignment when bone mass was lost. Additional benefits included the reduction of patient discomfort during evacuation to a general hospital.

Allied and Iraqi casualties showed a pattern of injury in keeping with a perceived conventional battlefield. This series has underlined the effectiveness of present day anti-personnel munitions and highlighted the continued requirement in the practice of military surgery for a clear understanding of the mechanism of wounding in war and the appropriate management.

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References

1. Ryan JM, Cooper GJ, Haywood IR, Milner SM. Field surgery on a conventional battlefield: strategy and wound management. *Ann R Coll Surg Engl* 1991; **73**: 13–20.
2. Ryan JM, Cooper GJ, Maynard RL. Wound ballistics: contemporary and future research. *J R Army Med Corps* 1988; **134**: 119–25.
3. Cooper GJ, Ryan JM. The interaction of penetrating missiles with tissues – some common misapprehensions and the implications for wound management. *Br J Surg* 1990; **77**: 606–10.
4. Kirby NG, Blackburn G, eds. *Field Surgery Pocket Book*. London: HMSO, 1983.
5. Jackson DS, Batty CG, Ryan JM, McGregor WSP. The Falklands war: army field surgical experience. *Ann R Coll Surg Engl* 1983; **65**: 281–5.
6. Broome G, Butler-Manuel A, Budd J, Carter PG. The Hungerford shooting incident. *Injury* 1988; **19**: 313–17.
7. Marcus NA, Blair WF, Shuk JM *et al.* Low velocity gunshot wounds to the extremities. *J Trauma* 1961; **1**: 354–60.
8. Coull JT. Military surgery. *Injury* 1990; **21**: 270–2.
9. Rautio J, Paavolainen P. Afghan war wounded: experience with 200 cases. *J Trauma* 1988; **28**: 523–5.
10. Zinman C, Reis ND. External fixation in wartime limb surgery. *Israel J Med Sciences* 1984; **20**: 308–10.
11. Trouwborst A, Weber BK, Dufour D. Medical statistics of battlefield casualties. *Injury* 1987; **18**: 96–9.
12. Behrens F, Searls K. External fixation of the tibia. Basic concepts and prospective evaluation. *J Bone Joint Surg [Br]* 1986; **68-B**: 246–54.
13. Coupland RM. Technical aspects of war wound excision. *Br J Surg* 1989; **76**: 663–7.

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Perineal injuries in children

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Over a 12-year period, 463 children under 13 years of age were treated for perineal injuries. The most common cause of injury was a fall astride, but motor vehicle trauma and rape were responsible for most of the severe and multiple injuries. Physical or sexual abuse was evident in 178 (38 per cent) of children, and four sustained injuries from forceful enema. Minor abrasions or first degree tears (88 per cent) and second degree tears (6 per cent) were sutured primarily or allowed to granulate with sepsis rates of 1·2 per cent and 14 per cent respectively. Twenty-nine (6 per cent) children sustained third degree lacerations; one died from secondary pelvic haemorrhage. In the 28 survivors, the outcome of primary (18) or delayed (ten) surgical repair was related to whether or not early defunctioning colostomy had been performed.

Although the high morbidity of compound pelvic fractures has long been recognized[1], much less attention has been focused on the associated perineal wounds themselves. In children particularly, the perineum may be injured by a variety of blunt or penetrating forces, sometimes resulting in wounds which are significant, both functionally and cosmetically. Sepsis, which may be due as often to delay in diagnosis and definitive treatment as to the degree of wound contamination, accounts for most complications and may necessitate prolonged hospitalization[2]. This report describes our experience over a 12-year period of children who sustained injuries to the perineum from a variety of causes.

Patients and methods

Examination of computerized hospital records, theatre registers and trauma unit record forms revealed that between January 1978 and December 1989, 463 patients (308 girls and 155 boys) under 13 years had been treated for perineal injuries at Red Cross Children's Hospital. Iatrogenic injuries and pelvic visceral injuries not involving the perineum itself were excluded. Information extracted from case notes included mechanism of injury, associated injuries, course and management in hospital, and any complications recorded on outpatient follow-up.

Results

Mechanisms of injury are listed according to sex in *Table 1*. Cause of injury by age is illustrated in *Figure 1*. The single most common cause of injury was a fall astride; objects of impact were mostly bicycle crossbars, beds, fences and concrete walls, and playground equipment. Four patients suffered anorectal injury as a result of forceful enemas administered via hosepipes (three) or a goat's horn (one). There was a clear history of physical or sexual assault in 178 children. Children who were raped (76) or sodomized (22) are grouped separately from those who were sexually molested without vaginal or anal penetration having occurred (51). Details of the vulval injuries sustained by the 126 girls who were raped or sexually assaulted are listed in *Table 2*. Routine vaginal swabs taken on admission yielded positive cultures of *Neisseria gonorrhoea* in four patients and *Trichomonas vaginalis* in one. Twenty-two patients, mostly infants, presented with perineal injuries for which no history was available.

Associated injuries (*Table 3*) were sustained mostly by motor vehicle accident victims and included 13 pelvic fractures of which eight were unstable, and two lumbar vertebral fractures. Three hollow viscus ruptures required emergency laparotomy. Other intra-abdominal injuries were treated non-operatively. Seven boys sustained urethral injuries: three contusions and four ruptures, three of the membranous and one of the penile

Table 1 *Causes of injury*

Cause	Males	Females	Total
Accidental			
Fall astride	42	101	143
Impalement	27	31	58
Road traffic accidents	8	17	25
Zipper injuries	23	0	23
Animal bites	9	1	10
Enema	2	2	4
Non-accidental			
Rape	–	76	76
Sexual molestation	1	50	51
Sodomy	16	6	22
Human bite	3	0	3
Blunt assault	21	5	26
Unknown	3	19	22
Total	155	308	463

Table 2 *Vulval injuries seen in 126 female victims of sexual abuse*

Injury	Number of patients*
Tear of posterior fourchette	59
Labial lacerations/contusions	20
Periurethral bruising	25
Tears of the hymen	45
Bruising of the hymen	9

* Many patients had two or more of the above injuries

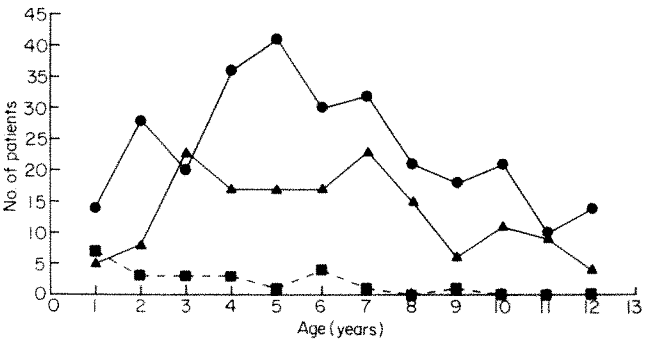

Figure 1 *Age distribution by cause of injury in 463 patients.* ●, *Accidental;* ▲, *non-accidental;* ■, *unknown*

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urethra. All four ruptures were confirmed by early ascending cystourethrography. Management consisted of emergency suprapubic cystostomy and elective cystoscopy and repair 4–6 weeks later.

Two patients (0·4 per cent), both pedestrian motor vehicle accident victims, died, one due to secondary haemorrhage from a disrupted pelvis (day 3) and the other from a severe closed head injury (day 2).

Classification and management

The perineal wounds have been grouped according to the following classification: *first degree* – abrasions or superficial lacerations involving the vulva, anal margin or perineal skin; *second degree* – tears involving the perivaginal or transverse perineal muscle but sparing the anal sphincters; *third degree* – compound lacerations involving the anal margin and sphincters.

The distribution of wounds by cause and severity is summarized in *Table 4*. First degree injuries were treated by simple suturing or regular cleansing with antiseptic solution so that healing by granulation could occur. Five children (1·2 per cent) returned after discharge from hospital with minor wound sepsis (three) or secondary bleeding (two). All five were successfully treated with antiseptic (Sitz) baths once venereal infection was excluded.

Second degree perineal tears were sustained by 28 (6 per cent) patients, all girls. All required examination and repair under general anaesthesia. In 17 cases, the tears extended into the vaginal vault and in two laparotomy was necessary to gain access to the upper extent of the injury. No colostomies were performed in this group, and minor wound sepsis without dehiscence occurred in only four patients, who were treated with frequent antiseptic baths.

In 29 patients (6 per cent), including two victims of forceful enema, examination under anaesthesia revealed third degree perineal tears. In 15 patients, the laceration extended into the anterior wall of the rectum. Massive secondary haemorrhage from a disrupted pelvis and consequent intravascular coagulopathy resulted in the death of one child before surgical repair could be undertaken. Of the remaining 28, 18 underwent primary repair, eight with divided sigmoid colostomy and ten without. The remaining ten patients presented after a delay or with grossly contaminated perineal wounds; treatment in this group consisted of wound debridement and irrigation with primary defunctioning colostomy (six) or without colostomy (four), pending delayed repair once the wounds were considered clean. All patients undergoing early or delayed repair received broad spectrum intravenous antibiotics commenced in theatre and continued for 2 to 5 days after operation. The incidence of septic complications is shown in *Table 5*. Two children required delayed colostomy, one due to a rectovaginal fistula which developed after primary repair of a rape injury, and a second who presented with a septic third degree tear 1 week after forceful enema.

Time spent in hospital for third degree tears was often dictated by the nature and severity of the associated intracranial or orthopaedic injuries, but mean time from injury to closure of colostomy (excluding two delayed colostomies) was 99 days in those who had primary repair of injuries and 182 days in those who underwent delayed repair. Patients with third degree injuries were followed up after discharge for 6 to 28 months (mean 16 months). Colostomies were eventually closed in all but one patient where gross distortion of the pelvic ring and scarring of the perineal floor precluded restoration of normal faecal continence. Other complications included temporary faecal incontinence in one 3-year-old boy and gonococcal vaginitis in two rape victims, both of whom were treated with amoxycillin and probenicid.

Discussion

Scant coverage in the literature to date[3–5] would suggest that perineal injuries are uncommon in children. Such injuries should, however, always be looked for, both when the history is specific (e.g. a fall astride), and following any high-velocity trauma, particularly if the pelvis has been fractured. The four anorectal injuries sustained as a result of forceful enema represent to our knowledge the first report of such a phenomenon in children. The enema is still highly regarded in traditional South African tribal medicine as a panacea for many ailments and the composition of the enema fluid and technique of administration appear to be empirical[6].

Examination under anaesthetic is usually necessary for adequate assessment of the child with an acute perineal injury[3] and should include routine sigmoidoscopy and speculum

Table 3 *Associated injuries*

	Accidental	Non-accidental
Head injury	2	–
Chest injury	2	1
Liver/spleen/kidney	4	–
Hollow viscus rupture	3	–
Fractures		
long bones	13	–
vertebral column	2	–
pelvis	13	–
Urethral injury	7	–
Peripheral nerve injury	3	–
Minor bruises and abrasions	16	24

Table 4 *Classification of perineal injuries by severity*

Cause	First degree	Second degree	Third degree	Total
Accidental	236 (1)	11	16 (1)	263
Non-accidental	148	17	13	178
Unknown	22	0	0	22
Total	406	28	29	463

Figures in parentheses denote patients who died

Table 5 *Septic complications following surgical management of third degree injuries**

	Accidental	Non-accidental	No. of complications	Management
Primary repair				
with colostomy	6	2	2	Antiseptic lavage only
without colostomy	1	9	5	Antiseptic lavage (4), delayed colostomy (1)
Delayed repair				
with colostomy	5	1	0	
without colostomy	3	1	1	Delayed colostomy

* $n = 28$

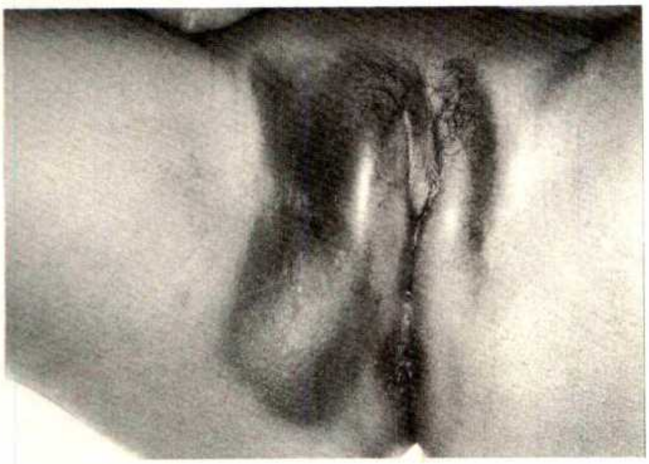

Figure 2 *Typical straddle injury in a 10-year-old girl showing asymmetric bruising of the perineum, labia and mons veneris*

examination of the vagina in girls. Preoperative cystourethrography should be requested if a urethral injury is suspected[5,7].

Although the 463 cases reported here represent a wide spectrum of paediatric perineal injuries, the vast majority (88 per cent) were minor injuries which required simple cleansing and dressings only, with an attendant sepsis rate of 1·2 per cent. It is notable, however, that 148 (37 per cent) of the 406 first degree injuries resulted from unequivocal physical or sexual abuse and that the medicolegal significance of detecting and documenting such injuries far outweighs the purely physical considerations[8]. Difficulty may be encountered in differentiating between accidental and non-accidental vulval injuries, particularly where the history is vague or unavailable, as was the case in 22 of our patients. Accidental injuries from blunt trauma tend to affect predominantly the soft tissues overlying the pubic bones, i.e. the anterior labia, urethra and clitoris (*Figure 2*), whilst contusions and tears of the hymen and posterior fourchette were the most common genital injuries seen in our female abuse victims. This distinction alone is less reliable where, for example, accidental impalement or self-instrumentation have occurred. When sexual abuse is suspected, much depends on the reliability of the history and its correlation with the physical findings[4].

The incidence of septic complications in this report was proportional to the extent of the wound, being 14 per cent in the second degree and 29 per cent in the third degree tears. Whereas simple postoperative hygiene was probably the most important factor affecting healing of the second degree tears, the outcome of the 28 surviving children with third degree tears was clearly related to whether or not an early defunctioning sigmoid colostomy was performed. Wound sepsis developed in only two of the 14 patients managed with early defunctioning colostomy while six out of 14 managed without colostomy developed septic complications, two necessitating delayed colostomy. This finding confirms previously reported experience with both adults[1,2] and children[3,5]. Maximum protection of the perineal wound from faecal soiling may be achieved by dividing the sigmoid loop into a proximal end colostomy and a distal mucous fistula and thoroughly irrigating the distal loop until the effluent is clean before proceeding to repair of the perineum itself. This was standard procedure in the patients reported here who underwent colostomy.

Even with faecal diversion, all open perineal wounds will inevitably become contaminated by anal and vaginal secretions and urine to a greater or lesser degree. Wound irrigation and debridement followed by primary repair should therefore be performed as soon as possible after resuscitation is complete and any life-threatening injuries have been attended to. This is particularly true where the perineal wound is associated with an underlying pelvic fracture, septic involvement of which may provoke fatal secondary haemorrhage (as occurred in one of the patients). Delay in proceeding to perineal wound closure may, however, be unavoidable in cases who present late after injury with established sepsis. Repeated wound debridement may be required before closure can be achieved without risk of septic dehiscence. Although we cannot offer any evidence that the functional or cosmetic results of delayed wound closure are inferior to those of primary repair, the psychological and economic effects of both prolonged hospitalization and later closure of colostomy associated with delayed repair argue in favour of the earliest possible definitive repair of major traumatic perineal injuries.

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References

1. Maull KI, Sachatello CR, Ernst CB. The deep perineal laceration – an injury frequently associated with open pelvic fractures. *J Trauma* 1977; **17**: 685–96.
2. Whallen TV, Kovalcik PJ, Wilson GC. Traumatic perineal laceration. *Am Surg* 1982; **48**: 145–8.
3. Sterioff S, Izant RJ, Persky L. Perineal injuries in children. *J Trauma* 1969; **9**: 56–61.
4. West R, Davies A, Fenton T. Accidental vulval injuries in children. *Br Med J* 1989; **298**: 1002–3.
5. Reinberg O, Yazbeck S. Major perineal trauma in children. *J Pediatr Surg* 1989; **24**: 982–4.
6. Wood R, Mills PB, Knobel GJ, Hurlow WE, Stokol JM. Acute dichromate poisoning after use of traditional purgatives. *S Afr Med J* 1990; **77**: 640–2.
7. Garrett RA. Paediatric urethral and perineal injuries. *Pediatr Clin North Am* 1975; **22**: 401–6.
8. Hobbs CJ, Wynne JA. Child sexual abuse – an increasing rate of diagnosis. *Lancet* 1987; **ii**: 837–45.

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Effect of initial biopsy procedure on prognosis in Stage 1 invasive cutaneous malignant melanoma: review of 1086 patients

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After treatment for primary clinical Stage 1 invasive cutaneous malignant melanoma, 1086 patients were followed for a minimum of 5 years from initial operation. Patient data were retrieved from the unit's melanoma registry; 96 (8·8 per cent) were treated initially by incisional biopsy, 292 (26·9 per cent) by narrow margin excision biopsy and 698 (64·3 per cent) by wide margin excision. Logistic regression analysis was performed to assess the statistical significance of the association between the various factors. The method of initial biopsy was related to maximal tumour thickness, age, and sex. Incisional biopsy rendered 38 out of 96 (40 per cent) lesions not fully assessable on current histopathological criteria, significantly higher than for the other biopsy techniques ($P<0.0001$). *Incisional biopsy did not adversely affect prognosis in terms of local recurrence and mortality. Prognosis was related to tumour thickness, age and sex of the patient, and not to biopsy technique. We recommend that all suspicious lesions should be submitted to excisional rather than incisional biopsy to avoid compromising the histological assessment, given the importance of maximal tumour thickness in determining treatment and prognosis.*

Several studies have addressed the question of whether or not there is a difference in outcome, measured in terms of local recurrence and mortality, related to the initial mode of biopsy of a cutaneous malignant melanoma[1–11]. None of the series so far reported has been large enough to produce statistically significant conclusions concerning the effects of incisional *versus* narrow margin excision biopsy and primary wide excision. The aim of the present study was to decide whether or not there was any difference in prognosis related to the mode of initial biopsy.

Patients and methods

The study comprised 1086 consecutive patients presenting with Stage 1 invasive cutaneous malignant melanoma to the Plastic Surgery Unit, Frenchay Hospital in the period 1967–1984, for whom there was a minimum follow-up period of 5 years. Patients with *in situ* lesions (Clark's level I) and lentigo maligna melanomas were excluded because these forms of the disease are known to behave less aggressively, as were patients dying from other causes within the follow-up period. Patients were also excluded when initial biopsy had been performed more than 3 months before definitive surgical treatment. Data were obtained from the unit's melanoma registry computerized database, details of which are given elsewhere[12]. From these records it was possible to identify the age and sex of the patient, nature of primary surgical treatment with width of excision margin, date of definitive excision, tumour type, maximal tumour thickness, and date and nature of local recurrence and death. Local recurrence was defined as that occurring within the scar or graft, at the edge of the scar or graft, or in transit between the scar or graft and the regional lymph nodes.

The three initial biopsy techniques to be compared were defined as follows:

1. Incisional biopsy: removal of part of the lesion, including biopsies where the tumour extended to the margin of the histological specimen.
2. Narrow margin excision biopsy: complete excision of the lesion where the narrowest clearance was ≤0·9 cm margin.
3. Primary wide excision: complete excision of the lesion where the mininum margin was ≥1·0 cm.

Analyses were based on the assumption that maximal tumour thickness, age and sex of the patient are important independent variables in determining prognosis. In doing so, the results of multivariate regression analyses of other authors who have sought to establish the relative prognostic value of numbers of clinical and histological variables were accepted[13,14]. Given maximal tumour thickness, age and sex as controlled factors for the three biopsy groups, an analysis of what differences, if any, existed between these groups in terms of their effect on prognosis was carried out. As maximal tumour thickness is probably the most important prognostic variable in cutaneous melanoma[15,16], it was postulated that a difference between the biopsy groups might only become apparent in the thinner lesions; lesions ≤4·0 mm were specifically examined.

Surgical policy over the review period has been to perform either primary wide excision on the basis of clinical appearance of the lesion, or narrow margin excision biopsy proceeding to definitive wide excision depending on the site and thickness of the lesion. Margins ranged up to 2 cm on the head and neck, 5 cm on the limbs and 10 cm on the trunk. During the latter part of the review period there has been a trend towards narrower margins of excision. Incisional biopsies were not specifically performed in this unit and were referred predominantly from elsewhere. Incisional biopsy may miss the thickest part of the lesion, and all those values of maximal tumour thickness where subsequent definitive excision of the lesion and histological assessment did not confirm the original reported thickness have been excluded from further analysis. Deep fascia was not routinely excised nor were prophylactic lymph node dissections routinely performed. Surgical wounds were closed primarily or by split thickness skin grafts, as appropriate.

Results were analysed using logistic regression analysis on the data set. The likelihood of recurrence or mortality occurring with a particular biopsy technique, having controlled for overall recurrence and mortality, age, sex and tumour thickness, was expressed as the odds ratio (odds ratio for which 95 per cent confidence interval includes 1·00 is considered not significant, i.e. no increase or decrease in likelihood of a particular event).

Results

Between 1967 and 1984, 1086 patients presented with primary clinical Stage 1 invasive cutaneous malignant melanoma; 698

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(64·3 per cent) patients underwent primary wide excision, 292 (26·9 per cent) underwent narrow margin excision biopsy and 96 (8·8 per cent) underwent incisional biopsy in the first instance.

Only cases where histological material has been available for inspection have been included in this study. There was a statistically significant difference in the number of samples not fully assessable produced by performing incisional biopsy: 40 per cent *versus* 5 per cent and 3 per cent for the narrow margin excision and primary wide excision groups respectively ($P<0{\cdot}0001$) (*Table 1*). Some specimens which were unassessable from the point of view of tumour type did have measurable maximal tumour thickness. The study yielded 1013 patients in whom maximal tumour thickness was available and these cases were used in all further analyses concerning tumour thickness. A description of the data set is given in *Table 2*.

Table 1 *Histological material not fully assessable in the biopsy groups studied*

Type of primary surgical treatment	*n*	Not fully assessable
Incisional biopsy	96	38 (40)
Minimal margin excision biopsy	292	15 (5)
Wide local excision	698	20 (3)

Values in parentheses are percentages

Table 2 *Basic data set*

Total number of patients	1086
Mode of initial biopsy	
Incisional	96
Narrow margin excision	292
Wide local excision	698
Maximal tumour thickness (mm)*	
Mean	2·77
Range	0·1–50·0
Age of patient (years)	
Mean	52·7
Range	12–96
Sex of patient	
Male	299 (27·5)
Female	787 (72·5)
Local recurrence	
Present	95 (8·7)
Not present	991 (91·3)
Mortality due to melanoma	
Death	420 (38·7)
Survival	666 (61·3)

Values in parentheses are percentages. * Tumour thickness not fully assessable in 73 patients

The incidence of local tumour recurrence is shown in *Table 3*. The rate was 13 out of 96 (14 per cent), 19 out of 292 (6·5 per cent) and 63 out of 698 (9·0 per cent) for the incisional biopsy group, the narrow margin excision biopsy group, and primary wide excision group, respectively. There was no difference between the biopsy groups in terms of local recurrence, having controlled for age, sex and maximal tumour thickness. The odds ratios were 1·67 for incisional biopsy, 0.73 for narrow margin excision biopsy and 0·81 for primary wide excision; none of these was significantly different from 1·00.

Death due to malignant melanoma over the study period is also detailed in *Table 3*. Although this shows that there is a difference in mortality rate between the biopsy groups (analysis of variance $P<0{\cdot}05$), the odds ratio showed no difference in mortality rate between the biopsy groups, having controlled for age, sex and maximal tumour thickness. (The odds ratios were 1·30 for incisional biopsy, 0·80 for narrow margin excision biopsy and 0·96 for primary wide excision; none of these was significantly different from 1·00.) Analysis of these data shows that there was a significantly raised mortality rate in the incisional biopsy group, but this was due solely to the significantly thicker tumours encountered in this group. Thus for a given thickness of tumour there was no difference in mortality rate between groups. It was noted that there was a significant difference in tumour thickness between those dying and those surviving ($P<0{\cdot}001$), which emphasizes the importance of tumour thickness on prognosis. There was a significant difference in mean maximal tumour thickness between the three treatment groups at the time of initial treatment ($P<0{\cdot}05$), but no difference in mean thickness by treatment group of those patients who died.

Patients who died had a mean maximal tumour thickness of 4·00 mm and, for the reason stated above, all lesions $\leqslant 4{\cdot}0$ mm were examined to see if a trend in mortality rate between groups could be identified for these thinner lesions (824 patients). Again there was no significant difference in local recurrence or mortality rates between biopsy groups.

In addition to the associations described in *Table 3*, there were found to be significant associations of maximal tumour thickness with sex, and with local recurrence and death ($P<0{\cdot}001$ for all). Patient age was significantly associated with death ($P<0{\cdot}001$) but not with local recurrence.

Discussion

The principal finding is that there is no increase in local recurrence or mortality rates related to the initial biopsy technique over a mininum 5-year review period. It was found that incisional biopsy had no detrimental effect on local recurrence or death over this period. However, incisional biopsy was associated with an unacceptably high rate of histological material that was not fully assessable. Nevertheless, it should be noted that a small percentage of tumours are not fully assessable for a variety of technical reasons not related to the initial surgery (2·9–5·1 per cent in this series). Incisional biopsy may miss the thickest part of the tumour, causing difficulties in prognostication and determination of suitable excision margins.

The effect of incisional biopsy on prognosis is controversial

Table 3 *Outcome and risk factors according to initial biopsy group*

	Incisional biopsy ($n=96$)	Narrow margin excision biopsy ($n=292$)	Wide local excision ($n=698$)	Biopsy groups combined ($n=1086$)	Level of significance*
Local recurrence	13 (14)	19 (6·5)	63 (9·0)	95 (8·7)	n.s.
Mortality	47 (48·9)	99 (33·9)	274 (39·2)	420 (38·7)	$P<0{\cdot}05$
Mean maximal tumour thickness (mm)	3·47	2·34	2·89	2·77	$P<0{\cdot}001$
Sex (male:female)	38:58	84:208	177:521	299:787	$P<0{\cdot}05$
Mean age (years)	59·9	49·8	52·9	52·7	$P<0{\cdot}001$

Values in parentheses are percentages. * Analysis of variance performed to determine whether or not there were significant differences between means of the three biopsy groups in relation to the other specified variables and it has been our aim to present data which will clarify the dispute. Rampen *et al.*[11] showed a possible detrimental effect on survival of incisional biopsy performed on 14 patients. Other surgeons are openly advocating incisional biopsy for diagnosis and operative planning purposes[17]. In a small series of eight incision biopsies (incomplete excisions) Heenan *et al.*[4] claimed lower mortality for this group after adjustment for tumour thickness. The principal objections to incisional biopsy have been a largely theoretical concern that the procedure would provoke tumour dissemination and a practical concern that incisional biopsy may prevent adequate histopathological analysis.

An earlier study from this unit[1] presented 19 cases initially treated by incisional biopsy. This series was judged too small to draw statistically significant conclusions on the effect of incisional biopsy. The present series yielded 96 cases having initial incisional biopsy, of which the maximal tumour thickness was available in 58. This is the largest series of incisional biopsies yet reported in the literature.

The rate of incisional biopsy was 8·8 per cent compared with 4·4–41 per cent reported in the literature[4,6,18]. The previous rate from this unit was 7 per cent[1]. Thus this unit's rate has not changed substantially despite an increased concern regarding the possible deleterious effect of incisional biopsy. The lower rates of incisional biopsy in other series may reflect a different definition of incision biopsy. Previous enquiry within this unit has shown that the majority of incisional biopsies are performed by other practitioners, i.e. by family doctors, dermatologists and surgeons in other specialities. There is no reason to think that this pattern has changed. It is difficult for those doctors who rarely deal with skin tumours to be confident of diagnosis and there is a persisting tendency to perform incisional biopsy when in doubt.

It has been shown that 90 per cent of local recurrence and 63 per cent of deaths following primary treatment of malignant melanoma occur within a 5-year period[19,20]. A minimum 5-year review period has been selected for the present study as the majority of recurrence has declared itself within this time. Furthermore, the objective in this study was to compare the prognosis between treatment groups, not to determine absolute rates of recurrence. There may be a bias in the study towards under-reporting of deaths in the community due to melanoma but attributed to some other cause, as few community deaths proceed to autopsy[21].

The higher rate of local recurrence in this study of 8·7 per cent, *versus* 1·5–6·7 per cent[2,8,9], is attributed to the following differences between the groups. The lower rates are quoted where lentigo maligna tumours were included, follow-up was less than 5 years, definition of local recurrence did not include in transit lesions, and where mean maximal tumour thickness was lower than in the present study. Furthermore, Veronesi *et al.* only recorded local recurrence if it was the first manifestation of recurrence[9]. The differences may also reflect the enthusiasm with which local recurrence is sought and recorded.

It has been demonstrated that the choice of biopsy technique does not affect prognosis in invasive cutaneous malignant melanoma over a 5-year follow-up period. Specifically, incisional biopsy has no adverse effect on outcome, but it compromises histological assessment including measurement of maximal tumour thickness.

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References

1. Griffiths RW, Briggs JC. Biopsy procedures, primary wide excisional surgery and long term prognosis in primary clinical stage I invasive cutaneous malignant melanomas. *Ann R Coll Surg Engl* 1985; **67**: 75–8.
2. Zeitels J, La Rossa D, Hamilton R, Synnestveldt M, Schultz D. A comparison of local recurrence and resection margins for stage I primary cutaneous malignant melanomas. *Plast Reconstr Surg* 1988; **81**: 688–93.
3. Lederman JS, Sober AJ. Does wide excision as the initial diagnostic procedure improve prognosis in patients with cutaneous melanoma? *J Dermatol Surg Oncol* 1986; **12**: 697–9.
4. Heenan PJ, Weramanthri T, Holman CD, Armstrong BK. Surgical treatment and survival from cutaneous malignant melanoma. *Aust NZ Surg* 1985; **55**: 229–34.
5. Landthaler M, Braun-Falco O, Leitl A, Kanz B, Holzel D. Excisional biopsy as the first therapeutic procedure *versus* primary wide excision of malignant melanoma. *Cancer* 1989; **64**: 1612–16.
6. Rampen FHJ, van der Esch EP. Biopsy and survival of malignant melanoma. *J Am Acad Dermatol* 1985; **12**: 385–8.
7. Urist MM, Balch CM, Soong S, Shaw HM, Milton GW, Maddox WA. The influence of surgical margins and prognostic factors predicting the risk of local recurrence in 3445 patients with primary cutaneous melanoma. *Cancer* 1985; **55**: 1398–1402.
8. Taylor BA, Hughes LE. A policy of selective excision for primary cutaneous malignant melanoma. *Eur J Surg Oncol* 1985; **11**: 7–13.
9. Veronesi U, Cascinelli N, Adamus J *et al.* Thin stage I primary cutaneous malignant melanoma. *N Engl J Med* 1988; **318**: 1159–62.
10. Rogers GS. Narrow *versus* wide margins in malignant melanomas. *J Dermatol Surg Oncol* 1989; **15**: 33–4.
11. Rampen FHJ, Van Houten WA, Hop WCJ. Incisional procedures and prognosis in malignant melanomas. *Clin Exp Dermatol* 1980; **5**: 313–20.
12. Briggs JC, Ibrahim NBN, Wickremeratchi T *et al.* A melanoma registry based on a computer-run word and data processing system. *Comput Biol Med* 1984; **14**: 245–52.
13. Clark WH, Elder DE, Guerry D *et al.* Model predicting survival in stage I melanoma based on tumour progression. *J Natl Cancer Inst* 1989; **81**: 1893–1904.
14. Meyskens FL, Donald HB, Parks B, Tong T, Loescher L, Moon TE. Cutaneous malignant melanoma (Arizona Cancer Center Experience). *Cancer* 1988; **62**: 1207–14.
15. Breslow A. Thickness, cross sectional areas and depth of invasion and node dissection in stage I cutaneous melanoma. *Ann Surg* 1975; **182**: 572–5.
16. Griffiths RW, Briggs JC. Incidence of locally metastatic ('recurrent') cutaneous malignant melanoma following conventional wide margin excisional surgery for invasive clinical stage I tumours: importance of maximal primary tumour thickness. *Br J Surg* 1986; **73**: 349–53.
17. Fisher JC. Safe margins for melanoma excision. *Ann Plast Surg* 1985; **14**: 158–61.
18. Roses DF, Ackerman AB, Harris MN *et al.* Assessment of biopsy techniques and histopathological interpretations of primary cutaneous malignant melanoma. *Ann Surg* 1979; **189**: 294–7.
19. Griffiths RW, Briggs JC. Long-term follow-up in cutaneous malignant melanoma: the relationship of maximal tumour thickness to disease free survival, disease recurrence and death. *Br J Plast Surg* 1984; **37**: 507–13.
20. Callaway MP, Briggs JC. The incidence of late recurrence (greater than 10 years): an analysis of 536 consecutive cases of cutaneous melanoma. *Br J Plast Surg* 1989; **42**: 46–9.
21. Hughes LE, Taylor BA. Biopsy procedure, primary wide excision and long term prognosis in primary clinical stage I invasive cutaneous malignant melanoma. *Ann R Coll Surg Engl* 1985; **67**: 269.

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Impalpable testis: testicular vessel division in treatment

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Between 1984 and 1989, 110 boys with 130 impalpable testes were investigated and treated. One hundred and six boys underwent laparoscopy. Twenty had bilateral impalpable testes and 13 had a palpable, but maldescended, testis on the other side. Forty-nine testes were absent and one atrophic testis was found in the scrotum. Twelve orchidectomies were performed. One child had a microvascular transfer procedure. The remaining 67 testes were treated by orchidopexy: 28 single-stage and 39 two-stage procedures. One of the single-stage and 29 of the two-stage orchidopexies included division of the testicular vessels. Twenty-three testes examined 12 or more months after staged testicular vessel division revealed a good result in 15.

Most undescended testes are palpable but the subgroup of impalpable testes represents a greater problem in assessment and management. The role of staged Fowler–Stephens orchidopexy has been evaluated in a cohort of boys with impalpable testes.

Patients and methods

Between 1984 and 1989, 110 boys with 130 impalpable testes were investigated and treated at the Children's Hospital, Birmingham, by reviewing the hospital records retrospectively.

One hundred and six boys underwent laparoscopy. Four boys had had a previous laparotomy and this was considered to be a contraindication to this examination. Twenty boys had bilateral impalpable testes and 13 had a palpable maldescended testis on the other side. Fifteen groin explorations with negative results had been performed elsewhere. Eighteen patients (16 per cent) had another significant abnormality (*Table 1*).

Forty-nine testes (38 per cent) were found to be absent and four boys had bilateral absent testes. One child had an unsuccessful microvascular transfer procedure. Twelve orchidectomies were performed; in ten the testis was markedly atrophic and histologically abnormal, one testis was abnormally shaped but histologically normal, and one was removed elsewhere and no further information was available. One atrophic impalpable testis was found in the scrotum. (Two of these boys had surgery at their referring hospitals after laparoscopy had shown the need for laparotomy.)

Orchidopexy was carried out on 67 testes: 28 single-stage and 39 two-stage procedures. Twenty-nine of the two-stage procedures included division of the testicular vessels as a modification of the Fowler–Stephens procedure[1]. The mean age at the time of the second operation was 6 years (range 1–16 years). Testicular vessel division was not performed if there had been a previous high retroperitoneal dissection. It was attempted only if assessment at laparoscopy, or occasionally laparotomy, showed the testis to be immobile with a short spermatic cord, suggesting that orchidopexy without division of the vessels would not be possible. The Fowler–Stephens test for bleeding from the incised testis after clamping of the testicular vessels was not performed. The mean interval between the two stages was 4 months (range 2–22 months). None of the testes was atrophic at the second operation.

Results

In one patient at the second operation, after division of the testicular vessels, it was impossible to bring the testis down into the scrotum because of a short vas and the testis was excised. It was noticed at operation that the testis had not atrophied after the first stage in this or any other patient. The other 28 testes were successfully positioned in the scrotum. Twenty-three of these testes have been examined more than 1 year after operation (mean 22 months, range 12–58 months). The results of the subgroup are given in *Table 2* and show that 15 have a good result with a normal sized scrotal testis.

Discussion

In 1959 Fowler and Stephens demonstrated that the testis could be adequately supplied by collateral arterial blood vessels if the testicular vessels were ligated[2]. They showed that there are constant communications from the vasa and cremasteric arteries, of which the vasa contribution was the most significant. All the collateral supply entered the testis by way of the main testicular artery and the importance of ligating the testicular vessels as far from the testis as possible was emphasized. They advocated a bleeding test after temporary clamping of the vessels to assess this collateral supply.

There are theoretical advantages to performing a staged procedure in which the testicular vessels are divided and the testis is left *in situ* to allow collaterals to develop before later

Table 1 *Other abnormalities in 110 boys with impalpable testes*

	No. of patients	No. of testes
Prune belly	3	6
Cardiac anomaly	3	3
Dystrophia myotonica	2	3
Hypospadias	2	2
Severe learning difficulties	2	2
Robinow's syndrome	1	2
Gastroschisis	1	2
Beckwith syndrome	1	1
Imperforate anus	1	1
Ileal atresia	1	1
Craniostenosis	1	1
Congenital adrenal hyperplasia	1	1
Total	18* (16%)	24* (18%)

*One patient had both hypospadias and a cardiac anomaly

Table 2 *Results of staged orchidopexy with testicular vessel division in 23 patients followed for more than 1 year*

	No. of patients
Normal size	
Normal position	14
High scrotum	1
Atrophied	8

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transfer to the scrotum. Initial results of this modification have been encouraging[1].

This review demonstrates a satisfactory result for 65 per cent of intra-abdominal testes not suitable for a standard orchidopexy. Kogan *et al.*[3] reported an 89 per cent success rate with a single-stage Fowler–Stephens technique, but subjects were excluded if they failed the Fowler–Stephens bleeding test. Using a staged approach in Birmingham it has been possible to include all immobile intra-abdominal testes with short vessels, which were considered to be unsuitable for standard orchidopexy.

The testicular vessels were divided approximately 2 cm from the testis[1,4] and it may be that leaving a longer stump of 4 to 5 cm, as recommended by Kogan *et al.*[3], combined with a staged procedure would give improved results.

References

1. Ransley PG, Vordermark JS, Caldamone AA *et al.* Preliminary ligation of the gonadal vessels prior to orchidopexy for the intra-abdominal testicle. A staged Fowler–Stephens procedure. *World J Urol* 1984; **2**: 266–8.
2. Fowler R, Stephens FD. The role of testicular vascular anatomy in the salvage of high undescended testes. *Aust NZ J Surg* 1959; **29**: 92–105.
3. Kogan SJ, Houman BZ, Reda EF *et al.* Orchiopexy of the high undescended testis by division of the spermatic vessels: a critical review of 38 selected transections. *J Urol* 1989; **141**: 1416–19.
4. Elder JS. Laparoscopy and Fowler–Stephens orchiopexy in the management of the impalpable testis. *Urol Clin North Am* 1989; **16**: 399–411.

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In situ femoropopliteal bypass: localization of arteriovenous fistulae using intraoperative Doppler ultrasonography

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The *in situ* technique of femoropopliteal bypass grafting has been in use for nearly 30 years[1] and is now known to yield results which are at least as good as the reversed saphenous vein method[2]. An often quoted advantage of the *in situ* method is that the natural taper of the non-reversed vein facilitates anastomosis to small crural vessels. An important disadvantage is the creation of arteriovenous fistulae which may lead to a steal of blood into the deep venous system at the expense of distal perfusion and which has also been associated with the development of localized areas of skin necrosis[3].

Arteriovenous fistulae can be identified in a number of ways. The most thorough is to expose the whole length of the saphenous vein to demonstrate all of its tributaries. However, even with this method it is possible to miss deep branches unless the vein is completely dissected free from its bed. Complete mobilization is unnecessarily time consuming because not all the branches found will be incompetent and therefore not all need ligation and division. The long incision required may heal poorly and is often very painful. Furthermore, the occurrence of fistulae has been noted in as few as one-sixth of cases[4], suggesting that a full length incision is not necessary in the majority of patients. It is more desirable to use only two main incisions together with a variable number of short incisions at the sites of fistula ligation. Peroperative arteriography can also be used to identify major fistulae, but is time consuming and by no means completely accurate.

Surgical technique

A method of detecting fistulae using an intraoperative ultrasonic Doppler probe has been developed. The instrument we have used is a standard hand-held Doppler ultrasound probe (Sonicaid BV102R, Sonicaid Ltd., Chichester, UK) placed in a sterile rubber glove. After completion of the proximal and distal anastomoses, the probe is placed against the proximal end of the graft and held in a position that gives a clear audible signal. The distal end of the graft is then gently occluded using a finger. If the graft has no fistulae, this manoeuvre should obliterate the flow and hence the audible signal. If flow continues then a fistula must exist between the probe and the point of occlusion (*Figure 1*). The graft can easily be occluded by finger pressure applied to the skin, and the fistula site can therefore be localized by moving the point of occlusion progressively more proximally until the Doppler signal is lost. An arteriovenous fistula localized this way can be ligated through a short incision.

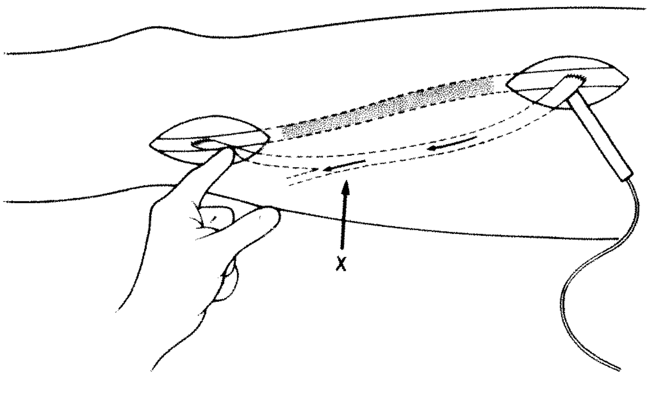

Figure 1 *Use of intraoperative Doppler ultrasound probe to detect an* in situ *graft arteriovenous fistula. Pressure at X obliterates the Doppler signal and localizes the fistula*

References

1. Hall KV. The great saphenous vein used in situ as an arterial shunt after extirpation of the vein valves. *Surgery* 1962; **51**: 492–5.
2. Harris PL, Tow TV, Jones DR. Prospective randomized clinical trial to compare in situ and reversed saphenous vein grafts for femoropopliteal bypass. *Br J Surg* 1987; **74**: 252–5.
3. Denton MJ, Hill D, Fairgrieve J. In situ femoropopliteal and distal vein bypass for limb salvage: experience of 50 cases. *Br J Surg* 1983; **70**: 358–61.
4. Cave-Bigley DJ, Ackroyd NA, Campbell H, Parry EW, Harris PL. Complications associated with in situ vein grafts for femoropopliteal bypass. *Br J Surg* 1984; **71**: 211.

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Technique and results of localization biopsy in a breast screening programme

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The techniques of ultrasonographic and hookwire localization biopsy of impalpable breast lesions detected by a large breast screening unit during its first year of operation are described. Hookwire localization (HL) was performed using mammography. Ultrasonographic localization (UL) was used for lesions readily detectable by ultrasonography by marking the skin directly over the lesion and calculating its depth below the surface. UL is not appropriate when microcalcification is the sole mammographic abnormality. Localization was required for 150 of the 191 (78·5 per cent) screen-detected lesions. HL was used for 94 (62·7 per cent) and UL for 56 (37·3 per cent). Four lesions were missed by HL, none by UL; 35 per cent of lesions removed by HL and 39 per cent by UL were malignant, giving benign:malignant biopsy ratios of 1·8:1 and 1·5:1 respectively. Only 22 per cent of the patients required overnight hospital stay. Localization biopsy plays a major role in the surgery for screen-detected lesions and, where applicable, UL is the technique of choice.

Numerous techniques for the localization and biopsy of impalpable mammographically detected breast lesions have been described, including double dye technique, carbon particle injection, triangulation, ultrasonography, ultrasonographically or radiologically guided needle and the currently favoured hookwire localization technique[1–4]. Double dye localization was originally the preferred method for impalpable lesions in Southampton[5] but has been superseded by hookwire localization (HL) and ultrasonographic localization (UL).

This paper describes the technique and results of localization biopsy performed on women presenting during the first year of breast screening in the Southampton and Salisbury Breast Screening Unit.

Patients and methods

Women aged between 50 and 64 years in the Southampton and Salisbury Health Authorities were invited to attend for screening following Forrest Report[6] guidelines, commencing in August 1988. Women with significant findings on single oblique-view mammography were recalled for further views, magnification views and ultrasonography as required. Microcalcifications alone were usually not imaged by ultrasonography because ultrasonography gives poor resolution of fine microcalcification[7]. Architectural abnormalities (mass lesions, densities and asymmetry) were imaged with a hand-held real-time technique, using a 7·5 MHz transducer on a Siemen's Sonoline apparatus. All suspicious lesions were referred for clinical assessment and, when palpable, fine needle aspiration cytology. Impalpable and dubiously palpable lesions underwent localization biopsy. Stereotactically guided cytological assessment was not used routinely[8], but was often used to assist HL.

If the lesion could be readily imaged by ultrasonography the patient was examined supine with the arm abducted and the skin overlying the lesion marked with indelible ink. The depth of the lesion below the skin was marked on the breast and in the patient's records with details of the localization procedure. Other lesions underwent HL using conventional[9,10] or stereotactic wire placement techniques.

Localization procedures were performed on the morning before surgery, which was carried out under general anaesthetic in the outpatient theatre. Inpatient stay was provided if there was a major medical illness, an anaesthetic problem, a need for multiple biopsies or no home support.

The breast incision was usually placed across the skin mark or wire entrance point. Incisions were oriented in a circumareolar direction except when this interfered with possible definitive surgery. The lesion was excised with an estimated 1 cm margin of clearance and confirmation obtained by radiology. The patient was not kept anaesthetized while awaiting the specimen radiography result if the surgeon was reasonably certain the lesion had been excised. A lesion was defined as missed if it was not visible on specimen radiography or pathology.

Results

Of 11 193 women screened in the first year 179 required operations on 191 lesions, and 150 lesions (78·5 per cent) from 141 women needed localization biopsy. Prior localization was not necessary for 41 (21·5 per cent) of the lesions for the following reasons: (1) the lesion was palpable (23 cases) or visible (two cases); (2) the lesion was not palpable but cytological examination proved malignancy (four cases) and definitive surgery could be undertaken on this basis; or (3) the lesion was not palpable but could be removed by subareolar resection (eight cases) or required segmental excision (four cases). The technique used was UL in 56 cases (37·3 per cent) and HL in 94 cases (62·7 per cent). Seven women had more than one localization biopsy performed under the same anaesthetic – three women had two HLs, one had three HLs and three had two ULs. One patient with a difficult lesion required both techniques on the same abnormality.

The indication for localization biopsy was microcalcification alone in 56 cases (37·3 per cent), an architectural abnormality alone in 71 (47·3 per cent) and both in 23 (15·3 per cent). In all, 22 (39 per cent) of the microcalcifications alone, 24 (34 per cent) of the architectural abnormalities alone and nine (39 per cent) of those lesions with both microcalcification and architectural abnormality proved to be malignant (*Figure 1*).

A total of 46 (82 per cent) of the ULs had an architectural abnormality alone and ten (18 per cent) had both architectural abnormality and microcalcification. Of these, 22 (39 per cent) proved malignant giving a benign:malignant ratio for UL of 1·5:1. Of the lesions localized by hookwire, 25 (27 per cent) had an architectural abnormality alone, 56 (60 per cent) microcalcification and 13 (14 per cent) both; 33 (35 per cent) of the HLs were cancers giving a benign:malignant ratio of 1·8:1. The overall benign:malignant localization biopsy ratio was 1·7:1.

All lesions localized by ultrasonography were satisfactorily excised but four (4 per cent) HLs were missed at surgery. In

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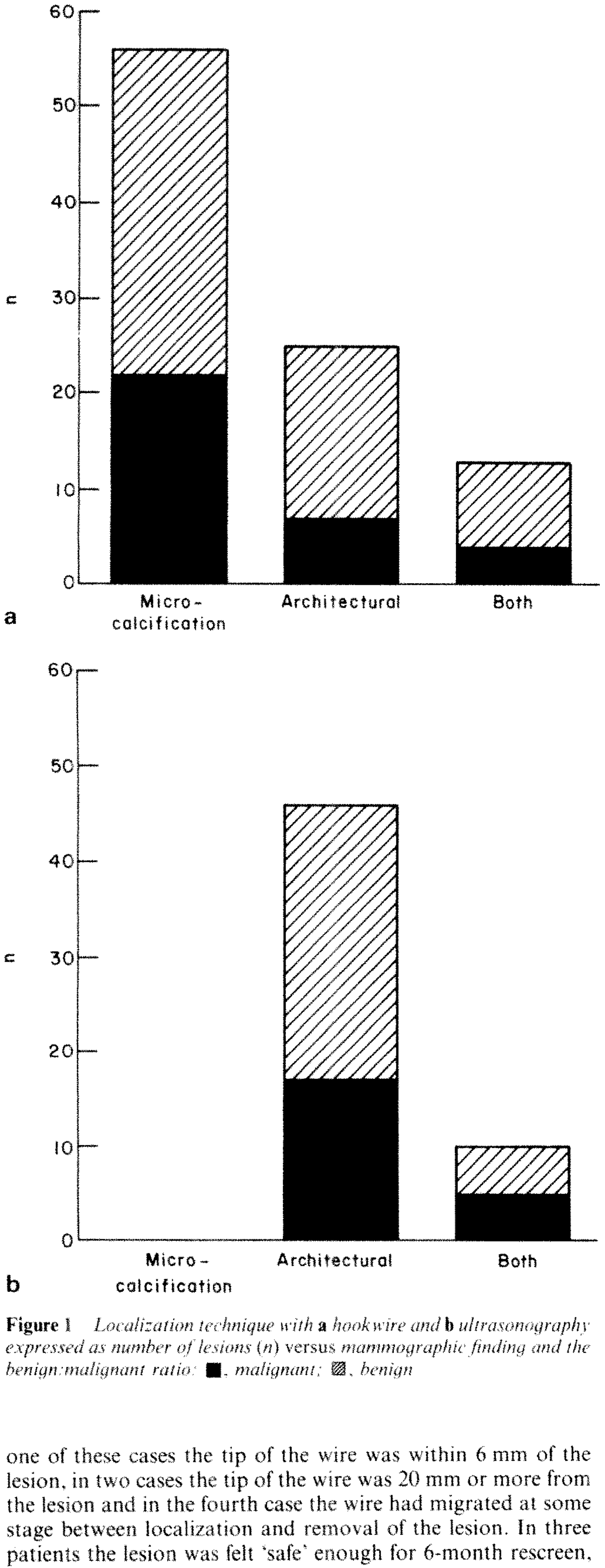

Figure 1 *Localization technique with* **a** *hookwire and* **b** *ultrasonography expressed as number of lesions* (*n*) versus *mammographic finding and the benign:malignant ratio:* ■, *malignant;* ▨, *benign*

one of these cases the tip of the wire was within 6 mm of the lesion, in two cases the tip of the wire was 20 mm or more from the lesion and in the fourth case the wire had migrated at some stage between localization and removal of the lesion. In three patients the lesion was felt 'safe' enough for 6-month rescreen, was unchanged and no further treatment was offered. The fourth patient had a benign lesion on relocalization biopsy. In two ULs it was uncertain on specimen radiography and pathology whether the lesion had been removed. Repeat mammography 6 months later confirmed removal of the lesion.

Of the 141 women undergoing localization biopsy, 102 (72·3 per cent) had their procedure as an outpatient and 39 (27·7 per cent) as inpatients, of which 31 (22 per cent) required overnight stay. The remaining eight were discharged later on the evening of surgery. The reasons underlying admission were: (1) a major medical problem in 24 (62 per cent); (2) an anaesthetic reason or inadequate home support requiring further observation in seven (18 per cent); (3) a surgical indication, e.g. multiple biopsies or a very wide excision, in eight (21 per cent) cases.

Discussion

These results demonstrate the major role localization biopsy plays in the treatment of screen-detected lesions.

UL was used in 37·3 per cent of cases and is the technique of choice when a lesion is readily imaged by ultrasonography. We and others[11] found that UL was much quicker for the radiologist to perform and it caused no pain for the patient who would otherwise need to have the breast compressed during mammography while a wire was inserted and positioned. There was no additional breast irradiation and a high success rate was demonstrated. The success rate was a little biased when compared with HL because small mass lesions were usually easily imaged and localized by ultrasonography and frequently became palpable at surgery. Microcalcifications required HL and less commonly became palpable at surgery. Although 82 per cent of UL lesions were characterized by architectural abnormalities alone – the abnormality with the highest overall proportion of benign lesions (66·2 per cent) – UL yielded the lower benign:malignant biopsy ratio. This result supports the view that ultrasonography adds information to that derived from mammography and helps select a group of women more likely to have malignant disease[12].

Reported problems of HL include wire transection[13] and migration[14]. Alternatives include use of a curved retractable J wire and needle system[15], use of hookwires with a thickened distal segment[16], use of a needle or cannula to stiffen the hookwire[17], and scalpel dissection which more readily allows needle palpation.

The overall success rate in this series was 97·3 per cent which compares well with reported rates of 92–98·5 per cent[18–20]. As others have noted[3], specimen and wound palpation are important as the lesion can often be palpated, indicating that the suspect area has been removed and giving information on the margin of clearance.

There are a number of advantages to excision with a margin: (1) the cosmetic result is little different from simple excision[21] and some women benefit by avoiding further surgery as a result of adequate primary excision of a cancer, 23 of 55 (42 per cent); (2) for microcalcification it is well established that the radiological and pathological extent of an abnormality varies[22] and in 18–24 per cent of cases the calcification may lie in benign areas and not be found in the malignant component of the lesion[23].

Some authors[1,24] have recommended that localization biopsies are performed as an inpatient procedure. This is costly and unnecessary in the majority of cases. In this series only 22 per cent of patients required overnight stay. None was admitted to hospital before surgery and there were no complications as a result of day case care. If local anaesthetic[18] is used an even higher proportion may be performed as day cases. In one recent report, however, one in five lesions was missed and 30 per cent of patients complained of intraoperative pain[21] by this method.

The techniques of ultrasonography and wire-guided biopsy of impalpable breast lesions should be used, but when lesions are visible on ultrasonography this is the method of choice.

Acknowledgements

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References

1. Leis HP, Cammarata A, LaRaja RD, Higgins H. Breast biopsy and guidance for occult lesions. *Int Surg* 1985; **70**: 115–18.
2. Wilhelm MC, Wanebo HJ. Technique and guidelines for needle localization biopsy of non-palpable lesions of the breast. *Surg Gynecol Obstet* 1988; **167**: 439–41.
3. Leinster SJ, Whitehouse GH, McDicken I. The biopsy of impalpable lesions of the breast. *Surg Gynecol Obstet* 1987; **164**: 269–71.
4. Mahoney L. Intraoperative localisation of occult breast tumours. *Can J Surg* 1985; **28**: 329–30.
5. Tate JTT, Royle GT, Guyer PB, Taylor I. X-ray and ultrasound localization of non-palpable breast lesions and difficulties in management. *J R Soc Med* 1987; **80**: 678–9.
6. Breast Cancer Screening: Report to the Health Ministers of England, Wales, Scotland and Northern Ireland by a Working Group chaired by Professor Sir Patrick Forrest. London: HMSO, 1987.
7. Kasumi F. Can microcalcifications located within breast carcinomas be detected by ultrasound imaging? *Ultrasound Med Biol* 1988; **14**(Suppl 1): 175–82.
8. Guyer PB. Starting from scratch – some problems with Forrest. *Clin Radiol* 1990; **41**: 1–2.
9. Frank HA, Hall FM, Steer ML. Preoperative localisation of nonpalpable breast lesions demonstrated by mammography. *N Engl J Med* 1976; **295**: 259–60.
10. Kopans DB, Meyer JE. Versatile spring hookwire breast lesion localiser. *AJR* 1982; **138**: 586–7.
11. Schwartz GF, Goldberg BB. Ultrasound: an alternative to X-ray guided needle localisation of non-palpable breast masses. *Ultrasound Med Biol* 1988; **14**(Suppl 1): 23–5.
12. Warwick DJ, Smallwood JA, Guyer PB *et al.* Ultrasound mammography in the management of breast cancer. *Br J Surg* 1988; **75**: 243–5.
13. Homer MJ. Transection of the localization hooked wire during breast biopsy. *AJR* 1983; **141**: 929–30.
14. Davis PS, Wechsler RJ, Feig SA *et al.* Migration of breast biopsy localisation wire. *AJR* 1988; **150**: 787–9.
15. Homer MJ. Localisation of nonpalpable breast lesions with the curved-end, retractable wire: leaving the needle *in vivo*. *AJR* 1988; **151**: 919–20.
16. Kopans DB, Lindfors K, McCarthy KA, Meyer JE. Spring hookwire breast localiser: use with rigid-compression mammographic systems. *Radiology* 1985; **157**: 537–8.
17. Kwasnik EM, Sadowski NL, Vollman RW. An improved system for surgical excision of needle-localised nonpalpable breast lesions. *Am J Surg* 1987; **154**: 476–7.
18. Petrovich JA, Ross DS, Sullivan JW, Lake TP. Mammographic wire localisation in diagnosis and treatment of occult carcinoma of the breast. *Surg Gynecol Obstet* 1989; **168**: 239–43.
19. Rusnak CH, Pengelly DB, Hosie RT, Rusnak CN. Preoperative needle localisation to detect early breast cancer. *Am J Surg* 1989; **157**: 505–7.
20. Norton LW, Pearlman NW. Needle localization breast biopsy: accuracy *versus* cost. *Am J Surg* 1988; **156**: 13B–15B.
21. Schwartz GF, Feig SA, Rosenberg AL, Patchefsky AS, Shaber GS. Localization and significance of clinically occult breast lesions: experience with 469 needle-guided biopsies. *Recent Results Cancer Res* 1984; **90**: 125–32.
22. Holland R, Hendriks JHCL, Verbeek ALM, Mravunac M, Schurmans Stekhoven JH. Extent, distribution and mammographic/histological correlations of breast ductal carcinoma *in situ*. *Lancet* 1990; **335**: 519–22.
23. Stock RJ, Kunschner A, Mazer J, Murphy A. Mammographic localization and biopsy: the experience of a gynecologic oncology group. *Gynecol Oncol* 1989; **33**: 172–6.
24. Michell MJ, Ebbs SR. Needle localisation of impalpable breast lesions. *Surgery (UK)* 1989; **67**: 1588–90.

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Routine examination of the vocal cords before and after thyroid and parathyroid surgery

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A prospective study of the value of routine examination of the vocal cords in 239 patients before and after thyroid or parathyroid surgery is presented. From the patient's history and voice the surgeon assessed before and after operation whether vocal cord examination was necessary or not. The surgeon's judgement was compared with the phoniatrician's report. All except one of the documented recurrent laryngeal nerve palsies were suspected by the surgeon. No additional important clinical information was gained by the laryngologist's examinations. Routine vocal cord examination in connection with thyroid and parathyroid surgery is probably not necessary.*

The mobility of the vocal cords is often routinely examined before and after thyroid or parathyroid surgery to detect patients in whom surgery has damaged the recurrent laryngeal nerve. Whether or not these few patients can be selected by simpler and cheaper means has not been studied.

Patients and methods

Two hundred and thirty-nine consecutive patients (201 women and 38 men; median age 49 years, range 15–84 years) undergoing thyroid or parathyroid surgery participated in the study. Twenty of them had previously undergone neck surgery and 73 were smokers.

Eleven surgeons performed the procedures and *Table 1* shows the type of operation and the histopathological diagnoses.

The operating surgeon interviewed the patient before operation and 2–3 days after operation, using a short and simple standardized questionnaire. The questions dealt with previous thyroid or parathyroid surgery, smoking habits, previous and present voice complaints, and singing voice. The strength of the voice was tested by asking the patient to shout 'hello' loudly. From the interview and without knowledge of the phoniatrician's report the surgeon decided whether damage to the recurrent laryngeal nerve had occurred and whether he or she considered vocal cord examination necessary. Every patient was investigated before and after operation by a phoniatrician or otorhinolaryngologist who was unaware of the surgeon's opinion. The surgeon's appraisal and the phoniatrician's report were then compared.

The function of the superior laryngeal nerve was checked with videofibrolaryngoscopy if nerve damage was suspected on clinical grounds.

Results

Table 2 compares the surgeon's opinion and the phoniatrician's report before operation. Two patients with thyroid malignancy had paralysis of the recurrent laryngeal nerve; both were suspected by the surgeon. Many patients complained of different laryngeal symptoms (intermittent hoarseness, pain when speaking, etc.) but these complaints were rarely associated with objective signs.

Table 3 compares findings after operation. All patients, except one, with damage to the recurrent laryngeal nerve were recommended a specialist's examination because of suspected voice pathology, and two had paralysis noted before operation. The exception deals with a young woman who complained of voice changes after operation; the surgeon did not believe her complaint.

After a median observation of 1 year, eight recurrent nerve paralyses had recovered and three persisted. None of the three patients had subjective problems with the voice at the time of follow-up. Two patients with recurrent laryngeal nerve injury before and after operation due to large thyroid malignancies had died.

Discussion

Vocal cord examination before and after thyroid or parathyroid surgery is routinely performed in most clinics in Scandinavia and in many other European and American clinics. A recent survey in Sweden reported that 54 of 86 (63 per cent) surgical clinics carried out such routine vocal cord examination. Seventeen did not perform any routine examinations at all

Table 1 *Diagnoses and types of operation*

	Type of operation					
Diagnosis	Unilateral subtotal lobectomy	Lobectomy	Bilateral subtotal lobectomy	Total thyroidectomy	Parathyroid exploration	Total
Parathyroid adenoma or hyperplasia	–	–	–	–	65	65
Nodular thyroid goitre	7	9	45	1	–	62
Hyperthyroidism	2	–	48	–	–	50
Thyroid adenoma	2	33	–	–	–	35
Thyroid cancer	–	4	–	17	–	21
Miscellaneous	4	1	–	1	–	6
Total	15	47	93	19	65	239

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* *A 'phoniatrician' is a subspecialty doctor in otolaryngology with an interest in laryngology. The specialty group is particularly active in Scandinavia, France, Germany and Eastern Europe.*

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Table 2 *Comparison between the surgeon's opinion and the phoniatrician's report before operation*

	Surgeon's opinion		
		Examination not indicated ($n=210$)	
Phoniatrician's opinion	Examination indicated ($n=29$)	Laryngeal symptoms and/or previous neck operation	No symptoms, no previous neck operation
Normal vocal cords	26	46	162
Palsy of recurrent laryngeal nerve	2	0	0
Reincke's oedema	1	1	0
Polyp	0	0	1

Table 3 *Comparison between the surgeon's opinion and the phoniatrician's report after operation*

	Surgeon's opinion	
Phoniatrician's report	Examination indicated ($n=31$)	Examination not indicated ($n=208$)
Normal vocal cords	8	196
Damage from the tube	8	9
Paralysis of recurrent laryngeal nerve	12	1
Damage to superior laryngeal nerve	2	1
Reincke's oedema	1	1

(J. Järhult, 1990, unpublished observations). In some hospitals the patient's voice is taped routinely.

The present study shows that the risk of missing a postoperative recurrent nerve palsy is small even if routine vocal cord examinations are omitted. From a simple questionnaire the surgeon can separate patients with suspected nerve damage from those who have normally functioning recurrent nerves. The majority of the recurrent nerve palsies recover spontaneously within a few months, making phoniatric treatment unnecessary. Treatment by speech therapists in the early postoperative period is instituted only if required by the patient's subjective discomfort. There is no evidence to show that early phoniatric treatment improves or shortens the healing of a damaged laryngeal nerve. There is no treatment available for the paralysis as such, but surgery is sometimes required if the vocal muscle remains denervated.

The legal aspects of damaging the laryngeal nerve may differ from country to country. In Sweden a patient with persistent recurrent nerve palsy will receive insurance compensation (£400–3000 depending on age) regardless of whether a routine laryngeal examination has been performed or not before operation.

The only arguments for retaining routine vocal cord examination before and after operation are education and research. Instead of routinely investigating the vocal cords, the surgeon should request a specialist's opinion only under certain circumstances. Since the highest frequency of 'silent' (=compensated) palsies of the recurrent laryngeal nerve is encountered among patients with previous thyroid or parathyroid surgery and in patients with thyroid malignancies, we consider that preoperative investigations are of value in these groups. Postoperative examinations are required if the surgeon or, particularly, the patient considers that the voice has changed after surgery.

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Prevalence of abdominal aortic aneurysm in Western Australia

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The prevalence of abdominal aortic aneurysm (AAA) in Western Australia was studied using health department mortality data. Age-standardized and age-specific mortality rates related to the disease were calculated for the period 1980–88. The mortality rate has risen by 36 per cent for men and 24 per cent for women. Most of this rise was due to an increase in non-hospital and emergency admission hospital deaths. The number of elective and emergency operations has also risen. Despite two decades of elective surgery, the mortality rate for AAA continues to rise. This rise is highly suggestive of an increasing prevalence. This contrasts with the decline in deaths from other manifestations of arteriosclerosis and provides support for a policy of screening for aneurysm.

When the epidemiology of abdominal aortic aneurysm (AAA) in Western Australia was first reported[1], it was noted that in addition to the expected increase in elective operations from 1971 to 1981, there was a continuing upward trend in the number of emergency operations. This observation raised the question: is AAA becoming more common in Western Australia?

Recent reports from other countries have shown an increase in diagnostic rates[2], operation rates[3] and mortality rates[4,5] for AAA over the past few decades. For reasons which will be discussed, not all of these reports have convincingly demonstrated a true increase in the prevalence of aneurysm. In an attempt to address this problem we have used health department data to identify any trends in the prevalence of aneurysm in Western Australia which, owing to its geographical isolation, is well suited to such epidemiological study.

Patients and methods

The health department data used throughout the study come from the hospital morbidity data system, the nature and scope of which has been previously described[6], and the mortality data system. The data for the mortality data system are read from a magnetic tape provided by the Registrar General of Western Australia. These data are based on death certificates coded and processed by the Australian Bureau of Statistics.

Deaths related to AAA are classified as either non-hospital deaths, the majority of which concern cases of ruptured AAA causing death before hospital is reached, or hospital deaths, which are further divided into emergency and elective categories. The classification of a patient as emergency or elective relates to the type of admission as coded by a hospital clerk at the time of admission to hospital.

International coding classifications 4413 and 4414 were studied: these cover ruptured and non-ruptured AAA. To exclude possible artifacts resulting from changes or errors in coding, the mortality rates for dissecting aortic aneurysms (4410), thoracic aneurysms (4411 and 4412) and 'unspecified' aortic aneurysms (4415 and 4416) were also examined. The current coding classification (ICD 9) was introduced to Western Australia in 1979 and data before this are difficult to compare, so the period from 1980 to 1988 was chosen for study. Age-specific and age-standardized mortality rates per 100 000 persons over 55 years of age were estimated. Men and women were analysed separately. These age-standardized rates were calculated by the direct method using the standard world population of Segi[7]. Population estimates were obtained from the Australian Bureau of Statistics, and were used as denominators for the calculations. In addition to mortality rates, the crude numbers of elective and emergency operations for AAA in patients over the age of 55 years have also been evaluated. The data were grouped by triennia to highlight trends which might otherwise have been obscured in year-by-year variation.

Results

The age-standardized mortality rate for AAA per 100 000 men over 55 years increased by 36 per cent from 33·61 deaths per year for 1980 to 1982 to 45·71 deaths per year for 1986 to 1988 (*Figure 1*). There was also a steady, albeit smaller (24 per cent), rise in the overall mortality rate in women over 55 years, from 8·94 during 1980–82 to 11·05 during 1986–88. As AAA is primarily a disease of men, the trends in male mortality data were examined in detail. Similar trends can be seen in the female data but the numbers are smaller and so less convincing. *Figure 2* shows the age-specific mortality rates in men.The overall mortality rate rose progressively over the study period for all ages with the exception of the 75–79-year age group. *Figure 2* also highlights the influence of rising age itself on mortality rate. Taking the whole period from 1980 to 1988, there was a 20-fold rise from the 55–59-year age group to the 70–74-year age group.

The nature of death in both men and women is shown in *Table 1*. The rise in total mortality rates over the years was caused primarily by an increase in emergency deaths (non-hospital and emergency hospital deaths). For men, the age-standardized mortality rate for elective cases more than doubled from 2·05 per 100 000 to 4·24 per 100 000. This was a relatively small contribution to the overall increase. The rise

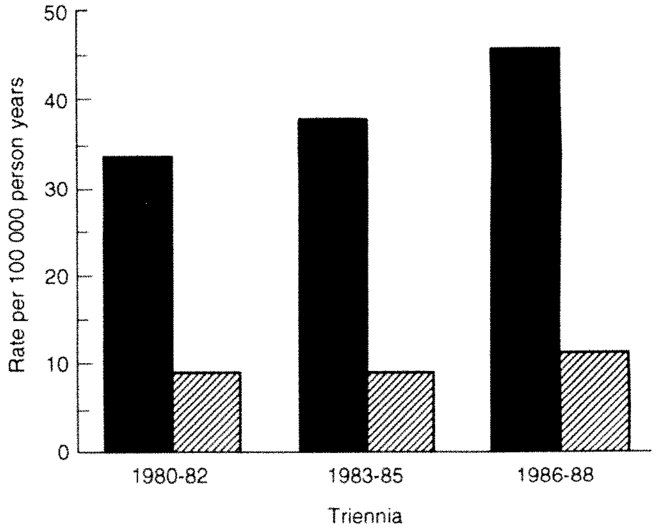

Figure 1 *All deaths from abdominal aortic aneurysm per annum in Western Australia for persons aged 55 years and over.* ▨, *Women;* ■, *men*

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in total deaths from AAA contrasts with a steady decline in deaths from ischaemic heart disease and stroke (*Figure 3*). The number of deaths from thoracic aneurysm remained stable over the study period and there was an increase in deaths from aortic dissection and 'unspecified' aortic aneurysms (*Table 2*).

The crude number of elective operations rose from an annual average of 40 operations during 1980–82 to 75 during 1986–88 (*Figure 4*), while emergency operations rose from an annual average of 71 during 1980–82 to 103 during 1986–88.

Discussion

We have demonstrated an increase in the age-standardized mortality rate for AAA between 1980 and 1988. Most of this increase appears to be due to a rise in AAA presenting with rupture, manifesting as a rise in emergency hospital deaths and non-hospital deaths. This has occurred despite an increase in elective surgery in Western Australia during the study period and over the previous decade[1]. Western Australia is geographically an ideal site for the study of aneurysm epidemiology; because of its isolation virtually no Western Australian patients have their AAA repaired outside the city of Perth. There are no vascular surgeons outside the metropolitan area, resulting in data which are as complete as is possible anywhere.

Diagnostic rate, operation rate and mortality rate have all been used in the past to analyse the epidemiology of AAA. Each of these parameters has its own set of errors, some of which are difficult to quantify. An increase in any one of these parameters does not necessarily imply a true increase in prevalence of the disease. Documenting the diagnostic rate in a community in which the number of radiologists and the number of ultrasound and computed tomographic scans may be increasing is fraught with difficulty. An increase in the diagnostic rate cannot be interpreted as an increase in true prevalence of AAA unless the data are standardized not only for age but also for AAA size. A report from the Mayo Clinic demonstrated an age-corrected increase in newly diagnosed AAAs of all sizes between 1950–60 and 1970–80[2]. Although the introduction of ultrasonography contributed to the tenfold rise in the diagnosis of small aneurysms, the authors felt that the increase in large (greater than 7 cm) aneurysms represented a true increase in incidence. It is, however, questionable that the referral rate to this tertiary centre was the same in the 1950s when aneurysm surgery was in its infancy, as in the 1970s when elective repair was well established.

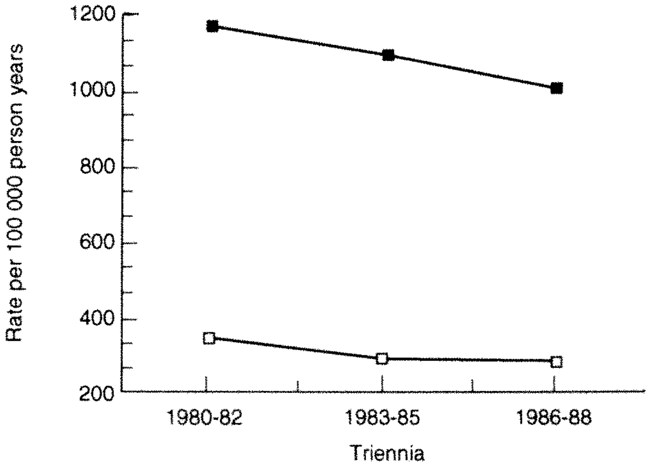

Figure 3 *Age-standardized mortality rate for cerebrovascular accident and ischaemic heart disease in males aged 55 years and over.* –□–, *Cerebrovascular accident;* –■–, *ischaemic heart disease*

Table 2 *Deaths from aortic dissection, thoracic aneurysm and 'unspecified' aneurysm in patients aged 55 years and over*

Year	Aortic dissection	Thoracic aneurysm	'Unspecified' aortic aneurysm
1980–82	33	24	66
1983–85	68	22	65
1986–88	48	22	83

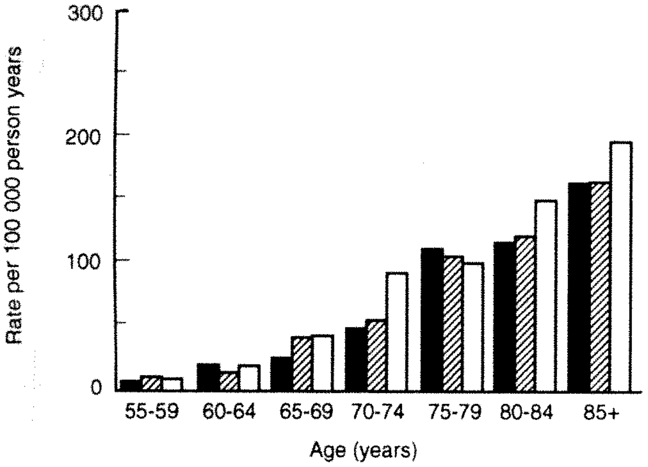

Figure 2 *Age-specific abdominal aortic aneurysm mortality rates for men aged 55 years and over.* ■, *1980–82;* ▨, *1983–85;* □, *1986–88*

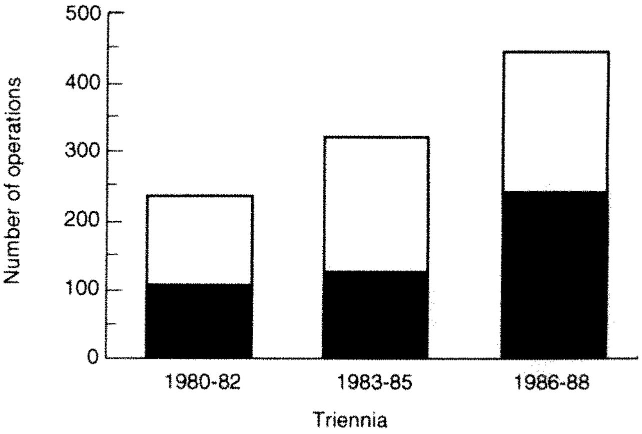

Figure 4 *Total number of operations for abdominal aortic aneurysm in patients aged 55 years and over.* ■, *Emergency;* □, *elective*

Table 1 *Age-standardized abdominal aortic aneurysm mortality rate per 100 000 aged 55 years and over, subdivided according to type of death*

	Hospital emergency		Hospital elective		Non-hospital		Total	
Year	Men	Women	Men	Women	Men	Women	Men	Women
1980–82	16·86	3·55	2·05	0·64	14·70	4·75	33·61	8·94
1983–85	17·71	2·89	5·67	0·16	14·53	6·08	37·91	9·13
1986–88	24·56	4·44	4·24	0·62	16·91	5·99	45·71	11·05

Many vascular centres have reported an increase in the number of elective operations for AAA[1,3,8]. We also found a continuing rise in elective operation numbers. This type of data is often expressed as crude numbers but, even when age-standardized, many factors contribute to rising elective operation rate. Not only are referral rate and diagnostic rate increasing but, as each decade passes, it is likely that smaller aneurysms are being repaired and higher risk patients are being accepted for surgery. Only if these disparate factors could be controlled would the elective operation rate reflect the true prevalence of AAA.

A rise in the rate of rupture of AAA despite increasing diagnosis and elective operation rate suggests a rise in overall prevalence, as this reflects a proportion of the undiagnosed aneurysms in the community. The number of emergency operations in Western Australia[1] rose steadily over the decade 1971–81, and this rise has continued relentlessly into the subsequent decade. Although some have reported a stable emergency operation rate[9], the majority of studies describe a rise in the crude number of ruptured aneurysms[3,10]. The age of many populations requires that this type of data be age-standardized to be meaningful. The incidence of rupture in Swansea, UK per 100 000 population over 65 years of age rose from 49 in 1974 to 89 in 1983[11]. Another age-standardized study from the UK demonstrated a rise in rupture rate for men over 55 years of 138 per 100 000 in 1981 to 173 per 100 000 in 1986[12].

The difficulties in relating changes in diagnostic or operative numbers to prevalence have led us to investigate the overall mortality rate from AAA as a more accurate indicator of disease prevalence. The total age-standardized mortality rate has clearly risen for both men and women over the period studied. This rise is largely due to an increase in emergency cases and is suggestive of a rise in true prevalence. If a decline in overall mortality rate had been demonstrated it might have been due to the benefits of elective surgery in reducing the number of rupturing aneurysms rather than a decline in prevalence. In this context, it is likely that the use of mortality rate to identify a rise in prevalence may well underestimate the magnitude of this rise; it is to be hoped that elective surgery has had some impact on overall mortality rate.

The possibility that the apparent rise in aneurysm deaths was an artifact resulting from coding or classification error was examined. The death rate from thoracic aneurysm was stable over the period studied while the death rates from aortic dissection and 'unspecified' aortic aneurysm both rose. It is, therefore, unlikely that the rise in deaths from AAA was due to the coding of other aortic pathology under AAA classification.

Age-standardized mortality data showed similar trends for both sexes, but the rates and trends for men were greater. This agrees with an age-standardized study documenting a 20-fold rise in mortality rate in men between 1950 and 1984 in England and Wales[5]. In view of this, the data for men were examined in more detail. The rise in mortality rate in men was noted in all age groups except the 75–79-year age group. This was due to an unusually high elective mortality rate for 1980 to 1982 in this age group (data not shown).

The distinction between emergency and elective hospital admission or death is subject to error due to coding mistakes in hospital data (e.g. a non-ruptured AAA admitted as an emergency). The rate at which these errors occur is likely to be constant and does not alter the observation that the total AAA mortality rate has risen.

The age-standardized elective mortality rate more than doubled over the study period, an observation which is cause for concern. The reason for this rise is unclear but it was probably due to an increase in elective operations without any decline in elective operative mortality rate. Although the rise in elective mortality rate has contributed to the total rise, it is a small contribution when compared to the rise in the emergency mortality rate. As it is unlikely that the diagnosis and referral rate of ruptured AAAs has improved between 1980 and 1988, we believe that the rise in overall deaths from AAA is a manifestation of a rising prevalence of AAA.

The basic tenet of AAA surgery is that elective repair of the aneurysm with an operative mortality rate of 2 to 6 per cent[1,13,14] is best undertaken before the disastrous event of rupture with a mortality rate of 75 to 94 per cent[12,15]. Despite a steady rise in the number of elective repairs in Western Australia, the supply of ruptured AAAs continues unabated and appears to be increasing. The prophylactic elective surgical repair rate in Western Australia is, therefore, currently inadequate; not enough AAAs are being detected before they rupture. The overall age-standardized mortality rate should be declining since nearly 1000 elective AAA operations have been performed in Western Australia over the last 20 years. The total number of patients at risk of rupture is increasing, not only because of the increase in the elderly population, but also because the true prevalence of AAA is rising.

The reason why AAA is becoming more common is unclear. Deaths from other manifestations of arteriosclerosis have decreased over the last three decades; e.g. deaths from myocardial infarction in Australia fell 30 per cent between 1968 and 1982[16]. Standardized death rates for both stroke and ischaemic heart disease fell steadily between 1980 and 1988 while AAA deaths rose. This trend has been confirmed in other countries[17]. One explanation for the increased incidence of AAA may be that patients with arteriosclerosis are no longer dying from its occlusive manifestations and are now living long enough to develop AAA. Patients operated on for aneurysmal disease of the aorta are 10 years older than those operated on for occlusive aortoiliac disease[18]. Subtle aetiological differences between aneurysmal and occlusive arteriosclerosis may also play a significant role in the diverging prevalences[19].

The case for elective aneurysm surgery is well established[8,20]. Once an AAA of significant diameter (probably greater than 5 cm) is diagnosed, it should be dealt with promptly unless there are major contraindications. The elective operative mortality rate of 2 to 6 per cent is unlikely to be improved upon, so the only means of improving survival is detection before rupture[4,20], and possibly improvement of referral rates for elective surgery[21].

The question of screening has been debated for some years[22,23]. It has been shown that the screening of at-risk groups, in particular men aged 65–74 years of age, is feasible[4]. The screening of patients with hypertension[24], peripheral vascular disease[25], or with a family history of AAA[26] may further improve the efficiency of screening programmes. Questions about cost and iatrogenic mortality of treating detected AAA have, however, been raised[22], and the long-term survival benefit of screening for AAA remains to be proven. With the present evidence that deaths from AAA are continuing to increase, a policy of screening for AAA in Western Australia will need to be considered; the survival benefit from screening would be easy to evaluate in this isolated community.

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References

1. Castleden WM, Mercer JC. Abdominal aortic aneurysm in Western Australia: descriptive epidemiology and patterns of rupture. *Br J Surg* 1985; **72**: 109–12.
2. Bickerstaff LK, Hollier LH, Van Peenen HJ, Melton III LJ, Pairolero PC, Cherry KJ. Abdominal aortic aneurysms: the changing natural history. *J Vasc Surg* 1984; **1**: 6–11.
3. Fielding JWL, Black J, Ashton F, Slaney G, Campbell DJ. Diagnosis and management of 528 abdominal aortic aneurysms. *Br Med J* 1981; **283**: 355–9.
4. Collin J, Araujo L, Walton J, Lindsell D. Oxford Screening

Programme for abdominal aortic aneurysm in men aged 65 to 74 years. *Lancet* 1988; **ii**: 613–15.

5. Fowkes FGR, Macintyre CCA, Ruckley CV. Increasing incidence of aortic aneurysms in England and Wales. *Br Med J* 1989; **298**: 33–5.
6. Holman CDJ, Brooks BH. *Inpatient hospital morbidity in Western Australia, 1971–1981*. Position Paper No. 2, Data Base Working Group, Steering Committee on the Review of Health Promotion and Health Education in Western Australia. Perth: Public Health Department.
7. Segi M. *Cancer mortality for selected sites in twenty-four countries (1950–57)*. Sendai: Tohoku University School of Medicine.
8. Pasch AR, Ricotta JJ, May AG, Green RM, DeWeese JE. Abdominal aortic aneurysm: the case for elective resection. *Circulation* 1984; **70**(Suppl 1): 1–4.
9. Hoffman M, Avellone JC, Plecha FR *et al.* Operation for ruptured abdominal aortic aneurysm: a community-wide experience. *Surgery* 1982; **91**: 597–602.
10. Jenkins AM, Ruckley CV, Nolan B. Ruptured abdominal aortic aneurysm. *Br J Surg* 1986; **73**: 395–8.
11. Ingolby CJH, Wujanto R, Mitchell JE. Impact of vascular surgery on community mortality from ruptured aortic aneurysm. *Br J Surg* 1986; **73**: 551–3.
12. Thomas PRS, Stewart RD. Abdominal aortic aneurysm. *Br J Surg* 1988; **75**: 733–6.
13. Campbell WB, Collin J, Morris PJ. The mortality of abdominal aortic aneurysm. *Ann R Coll Surg Engl* 1986; **68**: 275–8.
14. Rohrer MJ, Cutler BS, Wheeler HB. Long-term survival and quality of life following ruptured abdominal aortic aneurysm. *Arch Surg* 1988; **123**: 1213–16.
15. Johansson G, Swedenborg J. Ruptured aortic aneurysms: a study of incidence and mortality. *Br J Surg* 1986; **73**: 395–8.
16. Hobbs MST, Hockey RA, Martin CA, Armstrong BK, Thompson PL. Trends in ischaemic heart disease mortality and morbidity in the Perth Statistical Division. *Aust NZ J Med* 1984; **14**: 381–7.
17. Lilienfeld DE, Gunderson PD, Sprofka JM, Vargas C. Epidemiology of aortic aneurysms. I. Mortality trends in the United States, 1951 to 1981. *Arteriosclerosis* 1987; **7**: 637–43.
18. Tilson MD, Stansel HC. Differences in results for aneurysms vs. occlusive disease after bifurcation grafts. *Arch Surg* 1980; **115**: 1173–5.
19. Zarins CK, Glagov S. Aneurysms and obstructive plaques: differing local responses to atherosclerosis. In: Bergan JJ, Yao JST, eds. *Aneurysms. Diagnosis and Treatment*. New York: Grune and Stratton, 1982: 61–82.
20. Collin J. Elective surgery for abdominal aortic aneurysms. *Lancet* 1987; **i**: 909.
21. Cheattle TR, Grimley RP. Improving elective referral rate for abdominal aortic aneurysm. *Lancet* 1988; **ii**: 111.
22. Cooley DA, Carmichael MJ. Abdominal aortic aneurysm. *Circulation* 1984; **70**(Suppl 1): 5–6.
23. Collin J. Screening for abdominal aortic aneurysms. *Br J Surg* 1985; **72**: 851–2.
24. Lederle FA, Walker JM, Reinke DB. Selective screening for abdominal aortic aneurysms with physical examination and ultrasound. *Arch Intern Med* 1988; **148**: 1753–6.
25. Allardice JT, Allwright GJ, Wafula JMC, Wyatt AP. High prevalence of abdominal aortic aneurysm in men with peripheral vascular disease: screening by ultrasonography. *Br J Surg* 1988; **75**: 240–2.
26. Darling RC III, Brewster DC, Darling RC *et al.* Are familial abdominal aortic aneurysms different? *J Vasc Surg* 1989; 10: 39–43.

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Abdominal aortic aneurysm in 4237 screened patients: prevalence, development and management over 6 years

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An ultrasonography screening programme for detecting abdominal aortic aneurysm (AAA) in the community is described in which 7200 men and women aged between 65 and 80 years were contacted by letter. Of these, 4237 were screened; the aorta was visualized in 4122 and 179 AAAs of 3 cm or more in diameter were detected (4·3 per cent). Criteria for surgery are suggested and the results of their application prospectively over 6 years are discussed. Using these criteria, under 10 per cent of patients with ultrasonographically-detected AAA should require surgery for this condition provided ultrasonography follow-up is used.

Clinical detection of abdominal aortic aneurysm (AAA) is poor[1]. AAAs can rupture without previous symptoms[2] and emergency treatment carries a high mortality rate (30–55 per cent)[3–7]. By contrast, planned surgery has a low mortality rate (0–8 per cent)[3,5–7] and life expectancy after surgery is similar to that of the rest of the population of the same age[5,8,9]. In addition to the high mortality rate for emergency surgery, 34–64 per cent of patients with ruptured AAA die before reaching hospital[10–12] and many others die in hospital without reaching the operating theatre[10,13]. The overall mortality rate from rupture is, therefore, of the order of 80–94 per cent. Detection by ultrasonography screening of a general practice population would be expected to identify the aneurysms in the community before rupture and so reduce the overall mortality rate.

The prevalence of AAA has been reported in studies of small numbers of patients and in selected groups[14–17]. The natural history of small AAAs has been studied in poor-risk patients[18] and the relationship of rupture to aortic size deduced from post mortem studies[19]. Criteria for considering surgery for small AAA (less than 6 cm in diameter) have been based on observations of patients unfit for surgery[20] or from post mortem studies[19]. However, ultrasonography screening has established a new group of patients with detected disease and criteria for surgery in this group need to be developed. Ultrasonography scan follow-up of a small AAA allows expansion of the aneurysm to be detected[18,20,21]. When combined with aortic size and symptoms this may enable recognition of impending rupture.

A screening programme was set up to examine the prevalence and development of ultrasonographically-detected aneurysms. This has been in operation since 1984 and results over the first 6 years are presented.

Patients and methods

Patients aged 65–80 years were identified from a family doctor register and letters were sent out from their general practitioners inviting them to come to the screening clinic. Those who accepted the invitation were scanned in the local hospital. Patients were screened by an ultrasonographer with the assistance of a research nurse who obtained other data and answered queries.

At the first screening appointment a questionnaire regarding previous medical history, current medication and family history was completed. Additional observations of blood pressure, pulse, peak expiratory flow, height and weight were made. The size of the aorta was assessed using a B-mode linear ultrasonography machine (Siemens, Sunbury-on-Thames, UK). A central longitudinal examination of the aorta followed by transverse views at the renal level and at the level of maximum aortic diameter were made. Measurements of antero-posterior (AP) and transverse diameter were noted and a permanent record made of the abnormal vessels on the scan. An abnormal aorta was defined as one measuring 3 cm or more in diameter in either the AP or the transverse plane. Where possible, other organs such as the gallbladder, kidneys and liver were scanned. Patients were told that their family doctor would be informed if any abnormality requiring treatment was detected. When the family doctor was notified of an abnormal finding he or she became responsible for future management.

After consultation with the family doctor, patients with an enlarged aorta were offered further scans at intervals of 1 year if the diameter of the aorta measured less than 4·5 cm, and at intervals of 3 months if the aorta measured 4·5 cm or more (or more frequently if considered necessary). Patients were assessed in an outpatient clinic at or before the third scan and surgery was considered if one or more of the following criteria were met: (1) successive scans showed an expansion rate equivalent to more than 1 cm per year; (2) the aorta measured 6 cm or more in diameter; (3) symptoms attributable to the aneurysm were present.

Results

Letters were sent out to 7200 people and 4237 (1947 men and 2290 women) agreed to be scanned, giving an acceptance rate of 58·8 per cent. These 4237 comprised 2178 patients from a pilot study[22] and 2059 from the first year of the main study. The aorta could not be visualized in 115 (2·7 per cent) patients (62 men and 53 women). Of the remaining 4122, the maximum aortic measurement was less than 3·0 cm in 3943 (95·7 per cent) patients. Details of aortic size in the other 179 (4·3 per cent) are shown in *Table 1*.

Repeat scans have been performed in 103 people over a follow-up period ranging from 1 to 66 months (mean observation period 24 months). An increase in diameter was noted in AP, transverse or both planes in 57 (55·3 per cent).

Table 1 *Aortic size (≥3 cm) in 179 patients at initial scan*

	Aortic size (cm)				
	3–3·9	4–4·9	5–5·9	>6	Total
Men	101	27	8	12	148
Women	23	3	4	1	31
Total	124	30	12	13	179

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Table 2 *Outcome for patients reaching criteria for considering surgery*

	Reason for considering surgery				
Outcome	Initial diameter 6 cm	Reached 6 cm	Expansion ≥ 1 cm per annum	Symptoms	Total
Operation performed	6	5	2	2	15*
Operation planned but not yet performed	2	1	1	0	4
Died before surgery	2	1	0	0	3
Unfit for surgery	3	4	1	0	8
Patient declined	0	2	0	0	2
Follow-up with further scans	0	0	7	0	7
Lost to follow-up	0	0	3	0	3
Revised diagnosis	0	1	0	0	1
Total	13	14	14	2	43

* Plus one operation for iliac aneurysm

Table 3 *Deaths from all causes and from AAA within the Chichester district over 1 year*

	All causes			AAA			
Age (years)	Men	Women	Total	Men	Women	Total	Percentage of all causes
<65	257	159	416	1	0	1	0·2
65–80	677	554	1231	13	2	15	1·2
>81	451	866	1317	9	11	20	1·5
All	1385	1579	2964	23	13	36	1·2

AAA, abdominal aortic aneurysm

Forty-three patients were considered for surgery because the previously described criteria were reached, namely (1) 27 had an aortic diameter of 6 cm or more (13 initially, 14 on follow-up); (2) 14 had an increase in aortic diameter of more than 1 cm in a year but not reaching 6 cm; (3) two developed symptoms. The outcome for these patients is shown in *Table 2*.

Two patients were found to have a large iliac aneurysm, one of whom did not fulfil the criteria for AAA repair stated above. Both patients have been successfully treated.

Two operations have been performed because of rupture and both patients survived emergency surgery. One patient was treated early in the study for an AAA of 6 cm which ruptured 3 days before planned repair. The other had an enlarging symptomatic aneurysm but was considered unfit for planned surgery because of severe angina, dyspnoea and drop attacks. The aneurysm ruptured 4 years later when the diameter was 4·9 cm. Of patients with aortic diameter of 3 cm or more, 164 out of 179 have not had surgery and none has died from rupture.

Over the follow-up period, three patients who reached the criteria for operation have died following surgery for AAA; one 4 days after operation from a myocardial infarction, one 2 months after operation from ischaemic heart disease, and one after further surgery 3 years later, from bronchopneumonia. In all, including the three above, 21 patients out of 179 with detected AAA are known to have died during follow-up, but none from rupture. Three patients who declined screening are known to have died from ruptured AAA during the follow-up period. Follow-up of patients with detected AAA with at least one scan has shown 57 (55·3 per cent) increased in diameter in at least one plane. Of these, 24 (23·3 per cent) increased by more than 1 cm/year and nine (8·7 per cent) expanded to 6 cm in diameter.

Blood pressure was recorded in 3866 of those screened, and 442 (11·4 per cent) were found to be hypertensive (with a systolic pressure greater than 199 mmHg and/or diastolic pressure greater than 100 mmHg). Of those found to have AAA, 14·0 per cent were hypertensive, compared with 11·3 per cent of the remaining screened population. This difference was not significant ($\chi^2 = 0{\cdot}127$, $P = 0{\cdot}72$).

Table 4 *Place of death of patients dying from abdominal aortic aneurysm over a 1-year period*

Age (years)	Chichester hospital	Other hospital	Outside hospital	Total
<65	1	0	0	1
65–80	5	2	8	15
>81	5	1	14	20
Total	11	3	22	36

The incidences of other abnormalities detected were as follows: gallstones in 193 (4·6 per cent) patients, renal cysts in 96 (2·3 per cent), other cysts in 19 (0·4 per cent), and other abnormalities in 22 (0·5 per cent).

In addition to the screening programme, mortality statistics were examined. The cause of death over a 1-year period (week ending 2 December 1988 to week ending 24 November 1989) for the population in the catchment area of the Chichester District was recorded from information supplied by four local Registrars of Deaths. The total population for this district was 177 704, of whom 31 591 were aged 65–79 years and 10 091 were aged 80 years or more. Over a 1-year period 35 (1·4 per cent) of 2548 deaths of persons aged 65 years or more were recorded as due to AAA (*Table 3*). The place of death of patients with AAA, whether in the main general hospital, in other hospitals or outside hospital, was noted for the same population (*Table 4*).

Discussion

In 1984 when this screening programme started, the only prospective observation of patients with AAA was of those considered unfit for surgery[18,20,23]. Unlike earlier studies, the present observations concern patients who were not selected on a basis of fitness for surgery and who were not referred to hospital, i.e. a population selected only by age and acceptance of screening. In patients with an aortic diameter of 3 cm or more who were observed for up to 6 years, the diameter increased in at least one plane in 55 per cent. The increase was more than 1 cm per year in 23 per cent and 9 per cent expanded to 6 cm.

The prevalence of AAA when the study started was based on post mortem studies[19,24] and selected groups of patients with other medical conditions[16,23,25]. The present results show a prevalence of 4·3 per cent which is lower than those described in other studies of selected groups with known medical conditions[14,16,17]. The prevalence when women are excluded has ranged from 5·4 per cent[26] to 7·8 per cent[27], similar to that of 7·6 per cent found in the present study.

The diameter at which surgery is indicated for asymptomatic AAA has been a source of debate because of lack of knowledge of the natural history of the disease. However, AAAs of even less than 4 cm in diameter can rupture[28] and it has been suggested that operation be considered in patients with AAA of more than 4 cm in diameter[2].

In contrast, Bernstein and Chan[20] in a study on poor-risk patients with AAA of under 6 cm in diameter have shown that repeated ultrasonography scan observations and the application of specific criteria for surgery can result in a low (4 per cent) incidence of death from elective surgery or rupture. These authors also suggested that with ultrasonography scan observation, surgery may not be indicated in patients with AAA until a diameter of 6 cm is reached, there is rapid growth of the aneurysm or symptoms develop. At the start of the study in 1984 there were no data available regarding surgery on an unselected population with AAA identified by ultrasonography screening. Criteria similar to those suggested by Bernstein and Chan were, therefore, adopted.

Application of these criteria has resulted in 43 (24 per cent) out of 179 patients being considered for surgery; 15 of these 43 have actually undergone surgery. Twenty-one patients in whom AAAs were identified have died from causes other than rupture, and no patient in the screened group has died from rupture. The low incidence of rupture over 6 years suggests that the criteria were adequate for selecting patients at high risk of rupture. The results also indicate that patients with an AAA of under 6 cm and without symptoms may be followed with repeat ultrasonography scans. Provided expansion does not exceed 1 cm per year surgery may be avoided without an unacceptable risk of rupture.

Data on the place of death of those who died from ruptured AAA over 1 year support other studies[10–12] showing that the majority of patients with ruptured AAA die outside hospital. These findings confirm the need for detection of AAA in the community if the mortality rate from rupture is to be effectively reduced.

It was thought that widespread adoption of screening for AAA in the community might result in a marked increase in planned surgery if all the AAAs identified required treatment. However, the present results suggest that under 10 per cent of those patients with AAA of 3 cm or more will require surgery. It should, therefore, be possible to reduce the incidence of rupture without dramatically increasing the demand for planned operations. Nevertheless, before widespread screening is considered, a large-scale study of the rupture rate in a population requested for screening compared with the rate in a matched unscreened population is required.

The choice of age group for the screening programme was based on the observation that in our district 97 per cent of those who died from ruptured AAA were over the age of 65 years. Surgery for AAA over the age of 80 carries a high risk of death[29]. The group aged 65–80 years was therefore chosen for screening as that most likely to benefit from early detection of AAA.

An aortic diameter of 3 cm on ultrasonography scan was taken as constituting an AAA for screening purposes because (as discussed above) small AAAs can rupture. We also considered it important to include all those with an aorta above the normal range of less than 3 cm in diameter[30] to determine what proportion of these patients were at risk from aortic expansion and possible rupture. One patient in this study with an initial AAA of 3·2 cm in diameter was considered unfit for planned surgery and eventually ruptured her aneurysm. Five other patients who initially had aortic diameters of 3·0–3·9 cm have had their aneurysms expand by more than 1 cm per year and one patient has undergone surgery during the follow-up period. These cases confirm the need to include patients with an AAA of 3 cm in diameter in a follow-up programme. Out of 4237 people screened, only one patient with a normal aorta presented with rupture 42 months later, supporting a 3-cm diameter as the lower limit for follow-up.

Ultrasonography screening of patients aged over 65 years has resulted in a high rate of detection of existing AAAs. Selection for treatment is required to avoid unnecessary surgery because the majority of patients with AAA do not die from rupture. Selection should be done on the basis of suitability for operation, aneurysm size, expansion rate and symptoms. Using these criteria under 10 per cent of patients with AAA of 3 cm or more should require surgery for this condition provided ultrasound follow-up is employed.

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References

1. Robicsek F. The diagnosis of abdominal aneurysms. *Surgery* 1981; **89**: 275–6.
2. Collin J. Elective surgery for small abdominal aortic aneurysms. *Lancet* 1987; **i**: 909.
3. Campbell WB, Collin J, Morris PJ. The mortality of abdominal aortic aneurysm. *Ann R Coll Surg Engl* 1986; **68**: 275–8.
4. Amundsen S, Trippestad A, Viste A, Soreide O. Abdominal aortic aneurysms – a multicentre study. *Eur J Vasc Surg* 1987; **1**: 239–43.
5. Fielding J, Black J, Ashton F, Slaney G, Campbell DJ. Diagnosis and management of 528 abdominal aortic aneurysms. *Br Med J* 1981; **283**: 355–9.
6. Marsh CH. Experiences with abdominal aortic aneurysms in a district general hospital. *Ann R Coll Surg Engl* 1980; **62**: 294–6.
7. Castleden WM, Mercer JC. Abdominal aortic aneurysms in Western Australia: descriptive epidemiology and patterns of rupture. *Br J Surg* 1985; **72**: 109–12.
8. Appleberg M, Coupland GAE, Reeve TS. Ruptured abdominal aortic aneurysm: long-term survival after operation. *Aust NZ J Surg* 1980; **50**: 28–32.
9. Bardram L, Buchardt Hanson HJ, Dahl Hansen AB. Abdominal aortic aneurysms – early and late results after surgical and non-surgical treatment. *Acta Chir Scand* 1980; **502**: 85–93.
10. Armour RH. Survivors of ruptured abdominal aortic aneurysm: the iceberg's tip. *Br Med J* 1977; **ii**: 1055–7.
11. Mealy K, Salman A. The true incidence of ruptured abdominal aortic aneurysms. *Eur J Vasc Surg* 1988; **2**: 405–8.
12. Ingoldby CJH, Wujanto R, Mitchell JE. Impact of vascular surgery on community mortality from ruptured aortic aneurysms. *Br J Surg* 1986; **73**: 551–3.
13. Johansson G, Swedenborg J. Ruptured abdominal aortic aneurysms: a study of incidence and mortality. *Br J Surg* 1986; **73**: 101–3.
14. Twomey A, Twomey E, Wilkins RA, Lewis JD. Unrecognised aneurysmal disease in male hypertensive patients. *Int Angiol* 1986; **5**: 269–73.
15. Lindholm L, Ejlertsson G, Forsberg L, Norgren L. Low prevalence of abdominal aortic aneurysm in hypertensive patients: a population based study. *Acta Med Scand* 1985; **218**: 305–10.

16. Cabellon S, Moncrief CL, Pierre DR, Cavanaugh DG. Incidence of abdominal aortic aneurysms in patients with atheromatous arterial disease. *Am J Surg* 1983; **146**: 575–6.
17. Allardice JT, Allwright GJ, Wafula JMC, Wyatt AP. High prevalence of abdominal aortic aneurysm in men with peripheral vascular disease: screening by ultrasonography. *Br J Surg* 1988; **75**: 240–2.
18. Bernstein EF, Dilley RB, Goldberger LE, Gosink BB, Leopold GR. Growth rates of small abdominal aortic aneurysms. *Surgery* 1976; **80**: 765–73.
19. Darling RC, Messina CR, Brewster DC, Ottinger LW. Autopsy study of unoperated abdominal aortic aneurysms. The case for early resection. *Cardiovasc Surg* 1977; **56** (Suppl 2): 161–4.
20. Bernstein EF, Chan EL. Abdominal aortic aneurysm in high risk patients. *Ann Surg* 1984; **200**: 255–63.
21. Cronenwett JL, Sargent SK, Wall MH *et al.* Variables that affect the expansion rate and outcome of small abdominal aortic aneurysms. *J Vasc Surg* 1990; **11**: 260–8.
22. Scott RAP, Ashton HA, Kay DN. Ultrasound screening for abdominal aortic aneurysms: the results of screening in 2056 people. In: Strano A, Novo S, eds. *Advances in Vascular Pathology*, Vol 2. Netherlands: Elsevier Science Publications, 1989: 1299–301.
23. Szilagyi DE, Elliott JP, Smith RF. Clinical fate of the patient with asymptomatic aortic aneurysm and unfit for surgical treatment. *Arch Surg* 1972; **104**: 600–6.
24. Turk KAD. The post-mortem incidence of abdominal aortic aneurysm. *Proc R Soc Med* 1965; **58**: 869–70.
25. Karmody AM, Leather RP, Goldman M, Corson JD, Shah DM. The current position of non-resective treatment for abdominal aortic aneurysm. *Surgery* 1983; **94**: 591–7.
26. Collin J, Araujo L, Walton J, Lindsell D. Oxford screening programme for abdominal aortic aneurysms in men aged 65 to 74 years. *Lancet* 1988; **ii**: 613–15.
27. O'Kelly TJ, Heather BP. General practice-based population screening for abdominal aortic aneurysms: a pilot study. *Br J Surg* 1989; **76**: 479–80.
28. Russell AJ, Ward AS. Prognosis of abdominal aortic aneurysm. *Br Med J* 1990; **301**: 446.
29. Harris KA, Ameli FM, Lally M *et al.* Abdominal aortic aneurysm resection in patients more than 80 years old. *Surg Gynecol Obstet* 1986; **162**: 536–8.
30. Dixon AK, Lawrence JP, Mitchell JRA. Age related changes in the abdominal aorta shown by computed tomography. *Clin Radiol* 1984; **35**: 33–7.

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Ruptured aortic aneurysm: a proposed classification

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There is a wide variation in reported operative mortality rates for ruptured abdominal aortic aneurysm, ranging from 14 to 70 per cent. Although many factors influence this variation, such as the expertise and facilities available at an individual institution, considerable differences could be due to variations in the pattern of referral and the proportion of cases accepted for operation. In this paper a classification applicable to all patients with ruptured aortic aneurysm is proposed; it has been applied prospectively to 100 consecutive patients with ruptured abdominal aortic aneurysm referred to the Edinburgh Vascular Surgical Unit. The classification illustrates how surgical mortality rates ranging from 29 to 52 per cent may be reported using the same mortality data. Two major benefits may derive from the use of such a standard reporting system. Firstly, it allows management deficiencies to be identified easily and, secondly, it should facilitate comparison of results reported from different centres.

The prognosis after rupture of an aortic aneurysm is poor; more than 50 per cent of patients die in the community whether or not the correct diagnosis is made[1-4]. Even after operation, mortality rates are high (*Table 1*)[5-22].

Although the mean operative mortality rate of the 18 series in *Table 1* is 47 per cent, the range is from 21 to 70 per cent. Going back further in time, even lower mortality rates can be found, for instance 14 per cent in one 1979 series[23]. There are a number of possible reasons for this variation between institutions. For instance, it is probable that hospitals which deal with a large number of ruptured aneurysms, with the consequent development of specialized expertise by both surgeons and anaesthetists and the existence of a standardized and efficient channel for handling these patients, are more likely to produce better results.

Furthermore, hospitals that act as secondary referral centres may receive only patients who are haemodynamically stable, the less fit dying before arrival, whereas primary referral centres may receive sicker patients[8]. There may also be a selection bias in patient referral[24]. Variation in reported results may also reflect variation in transfer time to hospital, although evidence is sparse. Some believe that patients who are selected for transport and survive the journey usually have a contained rupture and therefore a better prognosis[24]; in at least one report[25] a higher mortality rate has been linked to delay. Other authors have failed to show any correlation between transport time and survival rate[26] or have suggested that the mortality rate for those travelling for less than 5 h is greater than for those travelling for more than 5 h[19].

Another important factor is case selection. It is generally accepted that the mortality rate after untreated ruptured aneurysm is almost 100 per cent[27]. This fact has led some to suggest that surgery should be attempted in almost all patients regardless of their condition and circumstances[6,9,21]. Others doubt the propriety of operating on patients over 70 years old who have been admitted in shock and who have serious concomitant disease. If a policy of selection is used, it is probable that the operative mortality rate will improve[28].

In many published series, information on patients who did not have an operation is absent[29]. Authors variously include all patients referred to the institution, only those who arrive alive, only those for whom operation is intended, only those who reach the operating theatre, or only those who survive operation and leave the operating theatre alive. Furthermore, when interpreting the results of operative intervention, in some early reports a clear distinction is not always made between aneurysms operated on urgently for symptoms and those operated on as an emergency for rupture[28,30-33].

All the factors so far discussed cause confusion in our understanding of reported results of intervention for rupture. A strict classification for ruptured aortic aneurysm is required which will allow the inclusion of all situations. It would allow specific areas of management weakness to be recognized and meaningful comparisons between results from different institutions to be made. Such a classification is proposed in this paper; it has been tested on a consecutive series of 100 ruptured abdominal aortic aneurysms.

Patients and methods

The Edinburgh Ruptured Aneurysm Classification (ERAC)

The classification must include all patients with ruptured abdominal

Table 1 *Reported operative mortality rates after ruptured abdominal aneurysm (1984–90)*

First author	Year	No. of cases	Operative mortality rate (%)
Cooley[17]	1984	77	21
Pasch[5]	1984	54	70
Fielding[19]	1984	198	43
Donaldson[20]	1985	81	43
Ruberti[9]	1985	238	53
Hernando[10]	1985	23	44
Crew[15]	1985	70	34
Campbell[6]	1986	52	56
Jenkins[7]	1986	178	33
Shackleton[22]	1987	106	40
Amundsen[18]	1987	114	63
Vohra[11]	1988	92	39
Martin[14]	1988	58	26
Thomas[16]	1988	75	55
Collin[22]	1989	75	36
Salo[21]	1989	47	70
Ivers[12]	1990	51	55
Ouriel[13]	1990	243	55
All series		1832	47 (mean)

Presented at the tripartite meeting of the Vascular Surgical Societies of Great Britain and Ireland, Holland and Canada held in London in November 1990

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Table 2 *The Edinburgh Ruptured Aneurysm Classification applied to 100 consecutive patients*

Location	Aneurysm class	Definition	No. of patients
Community	A	Death in community (aneurysm undiagnosed)	NK
	B	Death in community (aneurysm diagnosed)	NK
Peripheral hospital	C1	Death in peripheral hospital (autopsy diagnosis)	NK
	C2	Death or survival in peripheral hospital (not referred)	NK
	C3	Death in peripheral hospital (after referral)	1
In transit	D	Death in transit	1
Referral hospital (no operation)	E	Death in referral hospital (before decision to operate)	4
	F1	Death in referral hospital after decision not to operate*	19
	F2	Survive without operation for 30 days	0
	F3	Death in referral hospital after patient refused operation	1
Referral hospital (perioperative)	G1	Death in referral hospital emergency department after decision to operate	0
	G2	Death in transit to theatre in referral hospital	0
	G3	Death in theatre (on induction or before graft)	6
	G4	Death in theatre (after graft insertion)	3
Postoperative	H	Death in postoperative period	17
Survivors	S	Survival for 30 days	48

NK, not known; * this category should include all patients who are refused operation even if the patient is not transferred to the secondary (referral) hospital

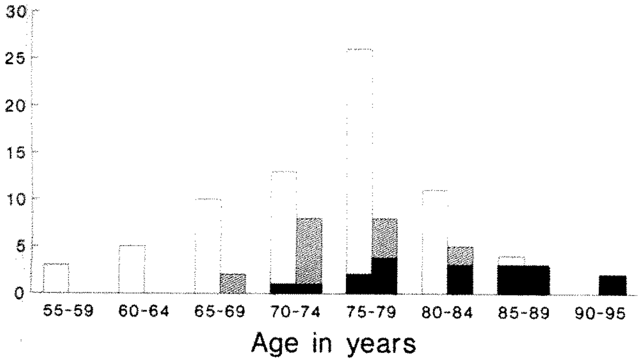

Figure 1 *The age–sex distribution of 100 consecutive patients with ruptured aortic aneurysm and suitability for operation.* □, *Male;* ▨, *female;* ■, *no operation*

Table 3 *Recorded contraindications in 19 patients considered unsuitable for surgery for ruptured aortic aneurysm*

Contraindication	No. of patients
Cardiac	10
Neurological	9
Age >80 years	10
Thoracoabdominal	2
Respiratory	2
Malignancy	1
Other	5

aortic aneurysm (*Table 2*). It therefore starts with the patient who dies undiagnosed in the community and continues in stages to the patient who survives operation for 30 days or to hospital discharge, whichever is the longer. Although the classification appears a little complex, a degree of sophistication is required to make it worthwhile.

It should be made clear that the term 'ruptured aortic aneurysm' includes only ruptured aneurysms associated with blood or haematoma lying outside the aorta; it does not include symptomatic aneurysms, even those operated on as an emergency. Furthermore, the classification should be applied from the point of view of the institution reporting the results, generally the secondary or referral hospital. It is also useful if data are simultaneously reported on the ratio between emergency and ruptured aneurysms carried out at the reporting institution and the percentage of primary *versus* secondary referrals.

Patients

This unit carries out all aortic aneurysm surgery for the Lothian Health Board Area, containing a population of approximately 750 000 people. It also acts as a secondary referral centre for the Borders Health Board and the Fife Health Board, with a combined population of a further 500 000. During the 16-month period from January 1989 to May 1990 a standard form was completed for every patient referred to the Edinburgh Vascular Surgery Unit, whether or not the patient: (1) was accepted for transfer; (2) did or did not arrive alive at the unit; and (3) did or did not have an operation. The data collected on the form included name, age, sex, source of referral, site of consultation and grade of surgeon making the decision. Also recorded was any contraindication to operation, specifically due to advanced age, or to cardiac, respiratory, neurological, renal or other disease. The final outcome was also noted. Data on patients operated on were obtained prospectively from the computerized operation and inpatient records. A series of 100 consecutive patients was recorded, comprising 64 primary referrals and 36 secondary referrals, containing 72 men (median age 74 years) and 28 women (median age 78 years) (*Figure 1*). During the study period the ratio of elective:ruptured aneurysm operations was 0·9:1·0.

Results

The ERAC, as set out in *Table 2*, was applied to 100 patients. The number of patients rupturing aneurysms in the community or in peripheral referring hospitals (classes A, B, C1, C2) was not known. Only two patients died after referral but before or during transit (classes C3, D); four died in the referral centre before a surgical decision could be taken (class E). Death supervened after a decision was taken not to offer operation in 19 patients (class F1), and this large group merits further consideration.

The reasons for not operating on the 19 patients in class F1 are shown in *Table 3*. In only two cases was advanced age alone the major contraindication to operation; both patients were over 90 years old. Cardiac problems, typically an evolving myocardial infarction or chronically intractable cardiac failure, formed the largest single group of contraindications, although in many instances it was a combination of factors that resulted in the decision not to operate. It is worthy of note that only 10 per cent of men but 38 per cent of women were considered unsuitable for surgery. This finding reflects the later age of presentation in women and the more frequent presence of severe concomitant disease.

No patient in the series survived without an operation (class F2). Apart from one who refused surgery (class F3), no patient died after the decision to operate but before anaesthesia (classes G1, G2), indicating an efficient transfer of patients within hospital and a ready availability of operating theatres. Nine patients died in the operating theatre (classes G3, G4) and 17

Table 4 *Percentage of patients with ruptured aneurysm considered unfit for surgery (class F1) in published series after 1980*

First author	Year	Minimum percentage
Amundsen[26]	1989	10
Campbell[6]	1986	15
Collin[22]	1989	12·5
Thomas[16]	1988	10
Marsh[30]	1980	26
Cox[31]	1981	58
Present series	1991	19

after the conclusion of the operation (class H). There were 48 survivors (class S).

The ERAC highlights both the multiplicity of ways of considering death after rupture of an aneurysm and the major distinction that must be made between mortality rate for the condition and operative mortality rate. For instance, 48 out of the 100 patients survived, and so 52 died, an overall mortality rate of 52 per cent, which would of course be even greater if information from classes A, B, C1 and C2 were available. On the other hand, grafts were inserted in 68 patients (classes G, H, S) of whom 20 (classes G4, H) died, an operative mortality rate of 20 out of 68, or 29 per cent. However if 'operative mortality' is applied to all patients in whom operation was proposed (G1–S), the operative mortality rate could be described as 35 per cent in this series.

Other ill-defined death rates can be constructed and have frequently been used to report results, for instance a mortality rate containing patients who might have had, but in the event did not actually have, an operation, e.g. any or all of classes C3–G2. The variable inclusion of these classes has been responsible for some of the variation in reported results between different centres.

Discussion

The use of the ERAC criteria has allowed a clear demonstration of the outcome for all 100 consecutive patients with ruptured aneurysm. ERAC data should be collected prospectively, if at all possible, because a number of patients who either do not reach hospital alive or who are turned down for operation will inevitably be lost in a retrospective series. The ERAC should make comparison between similar groups of patients from different centres straightforward and should allow methods of management to be scrutinized in appropriate detail.

The present series does not include patients who died in the community, with or without the correct diagnosis, before reaching hospital. There is now evidence from a number of studies suggesting that at least 50 per cent of all patients with ruptured aneurysms fall into this category (classes A and B)[3,34]. Any study to assess the size of this group will inevitably yield only an estimate, unless all sudden deaths are followed by an autopsy – a highly impracticable solution. This group is, in any event, irrelevant as far as hospital practice is concerned, because they die before referral. Its size will be reduced only by screening programmes for aneurysm followed by appropriate safe elective operation[35].

The design of the study did not allow accurate identification of all patients in the peripheral hospitals in Fife and the Borders who may have died from ruptured aneurysm with or without the correct diagnosis before referral to the vascular surgery unit. However, only three patients had operations for ruptured aneurysm in these peripheral hospitals over the period of the study.

It is clear that the most important group in terms of numbers is F1, containing those patients who are considered unsuitable for operation. Nineteen per cent fell into this group, which included patients who were referred by telephone and who were never directly spoken to or examined by vascular surgeons, but who were clearly unsuitable for surgery, for example a 92-year-old incontinent demented woman in a long-stay psychogeriatric home. Although some authors have suggested that all patients with ruptured aneurysm should be offered operation, an analysis of those studies that offer any relevant data demonstrates that 10–58 per cent do not undergo operation (*Table 4*). These published figures are likely to be an underestimate, as in many series the data have been collected retrospectively.

A main advantage of the prospective use of the ERAC is that it allows the identification of areas of management that could be improved – a fundamental step in audit. For the effective treatment of these extremely ill patients, the availability of efficient transport, adequate resuscitation, blood transfusion and intensive care facilities are needed as well as rapid access to an operating theatre staffed by senior surgical and anaesthetic personnel. By documenting the site and type of death of all patients, any excess mortality due to inadequate resources can be identified and corrected. Furthermore, continuous use of the ERAC would allow assessment of the benefits of any change in the provision of facilities for managing patients with ruptured aneurysms.

The use of the ERAC has shown clearly how, depending on which group is selected, the mortality rate associated with ruptured aneurysm could be presented as anywhere from 29 to 52 per cent. The operative mortality rate for those considered suitable for operation (groups G1 to S) was 35 per cent, similar to that previously published from this unit[7].

The ratio between operations for elective and ruptured aneurysm was 0·9:1, which is relatively low. This figure may, in part, be accounted for by the fact that, although virtually all patients with ruptured aneurysm are referred to the central vascular unit, a number of elective aneurysms are operated on in the district general hospitals in the neighbouring areas.

In summary, the prospective use of the Edinburgh classification allows an assessment of the degree to which referral pattern, transport distance and case selection have influenced the reporting of operative mortality rate for ruptured abdominal aortic aneurysm. It also aids in the identification of any shortcomings in the provision of facilities for the management of this life-threatening condition.

References

1. Ingolby CJH, Wujanto R, Mitchell JE. Impact of vascular surgery on community mortality from ruptured aortic aneurysms. *Br J Surg* 1986; **75**: 551–3.
2. Johansson G, Swedenborg J. Ruptured abdominal aortic aneurysms: a study of incidence and mortality. *Br J Surg* 1986; **73**: 101–3.
3. Armour RH. Survivors of ruptured abdominal aortic aneurysm: the iceberg's tip. *Br Med J* 1977; **2**: 1055–7.
4. Talbot S, Langman MJS. Epidemiological features of ruptured dissecting and saccular aneurysms. *Postgrad Med J* 1972; **48**: 414–18.
5. Pasch AR, Ricotta JJ, May AG *et al.* Abdominal aortic aneurysm: the case for elective resection. *Circulation* 1984; **70**(Suppl 1): 1–4.
6. Campbell WB, Collin J, Morris PJ. The mortality of abdominal aortic aneurysm. *Ann R Coll Surg Engl* 1986; **68**: 275–8.
7. Jenkins AM, Ruckley CV, Nolan B. Ruptured abdominal aortic aneurysm. *Br J Surg* 1986; **73**: 395–8.
8. Collin J, Murie J, Morris PJ. Two year prospective analysis of the Oxford experience with surgical treatment of abdominal aortic aneurysm. *Surg Gynecol Obstet* 1989; **169**: 527–31.
9. Ruberti U, Scorza R, Biasi GM, Odero A. Nineteen year experience on the treatment of aneurysms of the abdominal aorta: a survey of 832 consecutive cases. *J Cardiovasc Surg* 1985; **26**: 547–53.
10. Serrano Hernando FJ, Paredero VM, Del Rio A *et al.* Abdominal aortic aneurysms. Results of surgical treatment. *J Cardiovasc Surg* 1985; **26**: 539–46.
11. Vohra R, Abdool-Carrim ATO, Groome J, Pollock JG. Ruptured aortic aneurysms: postoperative complications and their management. *Ann Vasc Surg* 1988; **2**: 114–19.

12. Ivers CR, Bourke BM. Elective aneurysm repair and the incidence of aortic rupture in an ageing population. *Aust NZ J Surg* 1990; **60**: 203–7.
13. Ouriel K, Geary K, Green RM, Fiore W, Geary JE, DeWeese JA. Factors determining survival after ruptured aortic aneurysm: the hospital, the surgeon and the patient. *J Vasc Surg* 1990; **11**: 493–6.
14. Martin RS, Edwards WH, Jenkins JM, Edwards WH, Mulherin JL. Ruptured abdominal aortic aneurysm: a 25 year experience and analysis of recent cases. *Am Surg* 1988; **54**: 539–43.
15. Crew JR, Bashour TT, Ellertson D, Hanna ES, Bilal M. Ruptured abdominal aortic aneurysm: experience with 70 cases. *Clin Cardiol* 1985; **8**: 433–6.
16. Thomas PRS, Stewart RD. Abdominal aortic aneurysm. *Br J Surg* 1988; **75**: 733–6.
17. Cooley DA, Carmichael MJ. Abdominal aortic aneurysm. *Circulation* 1984; **70**(Suppl 1): 5–6.
18. Amundsen S, Trippestad A, Viste A *et al.* Abdominal aortic aneurysms – a national multicentre study. *Eur J Vasc Surg* 1987; **1**: 239–43.
19. Fielding JWL, Black J, Ashton F, Slaney G. Ruptured aortic aneurysms: postoperative complications and their aetiology. *Br J Surg* 1984; **71**: 487–91.
20. Donaldson MC, Rosenberg J, Bucknam CA. Factors affecting survival after rupture abdominal aortic aneurysm. *J Vasc Surg* 1985; **2**: 564–70.
21. Salo JA, Perhoniemi VJ, Mauri JA, Lepantalo MD, Mattila PS. Prognosis of patients over 75 years of age with a ruptured aortic aneurysm. *World J Surg* 1989; **13**: 484–7.
22. Shackleton CR, Schechter MT, Bianco R, Hildebrand HD. Preoperative predictors of mortality risk in ruptured abdominal aortic aneurysm. *J Vasc Surg* 1987; **6**: 583–9.
23. Lawrie GM, Morris GC Jr, Crawford ES *et al.* Improved results of operation for ruptured abdominal aortic aneurysms. *Surgery* 1979; **85**: 483–8.
24. Soreide O. Abdominal aortic aneurysm – by whom? *Eur J Vasc Surg* 1990; **4**: 333–4.
25. Yashar JJ, Indeglia RA, Yashar J. Surgery for abdominal aortic aneurysms. *Am J Surg* 1972; **123**: 398–405.
26. Amundsen S, Skjaerven R, Trippestad A *et al.* Abdominal aortic aneurysms – a study of factors influencing postoperative mortality. *Eur J Vasc Surg* 1989; **3**: 405–9.
27. McGregor JC. Unoperated ruptured abdominal aortic aneurysm: a retrospective clinico-pathological study over a 10 year period. *Br J Surg* 1976; **63**: 113–16.
28. Christenson J, Eklof BO, Gustafson I. Abdominal aortic aneurysms: should they all be resected? *Br J Surg* 1977; **64**: 767–72.
29. Ruckley CV. Aneurysm surgery in the over-eighties. In: Greenhalgh R, Mannick JA, eds. *The Cause and Management of Aneurysms.* London: W.B. Saunders, 1990: 327–37.
30. Marsh CH. Experiences with abdominal aortic aneurysms in a district general hospital. *Ann R Coll Surg Engl* 1980; **62**: 294–6.
31. Cox R, Ware CC. Abdominal aortic aneurysms in a district general hospital. *Ann R Coll Surg Engl* 1981; **63**: 177–80.
32. Baker WH, Munns JR. Aneurysmectomy in the aged. *Arch Surg* 1975; **110**: 513–17.
33. Castleden WM, Mercer JC, Members of the West Australian Vascular Service. Abdominal aortic aneurysms in Western Australia: descriptive epidemiology and patterns of rupture. *Br J Surg* 1985; **72**: 109–12.
34. Mealy K, Salman A. The true incidence of ruptured abdominal aortic aneurysm. *Eur J Vasc Surg* 1988; **2**: 405–8.
35. Collin J, Araujo L, Lindsell D. A community screening programme for abdominal aortic aneurysms. *Eur J Vasc Surg* 1988; **2**: 83–5.

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Announcement

Association of Surgeons in Training

Membership of the Association is open to all senior registrars holding accredited posts in general surgery, urology, plastic surgery, neurosurgery, orthopaedics, cardiothoracic surgery and paediatric surgery. Registrars in the above specialties who are 2 years post-fellowship may also apply. The Association represents the views of members on all matters relevant to surgical training and also holds scientific and social meetings. If you are not a member please contact the Secretary, Barney Harrison, 6 Kyveilog Street, Pontcanna, Cardiff CF1 9JA, for details of membership, local representatives and forthcoming meetings. The next AGM will be held in Oxford, 19–21 September 1991.

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Detection and characterization of arterial thromboses using a platelet-specific monoclonal antibody (P256 Fab′)

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Arteriography does not reliably distinguish between acute and chronic arterial occlusions. Seventeen patients with acute lower limb ischaemia were investigated by arteriography and by imaging with a platelet-specific monoclonal antibody (P256 Fab′); 20 MBq ^{111}In-labelled P256 Fab′ was administered intravenously and patients were imaged at intervals of between 20 min and 24 h. Thirteen patients were subsequently treated with intra-arterial thrombolysis. In six the images showed foci of increased uptake of ^{111}In-labelled P256 Fab′ and the corresponding arterial segment was recanalized. Patency to 30 days was maintained in four cases. Seven patients had negative scans, only four of whom achieved lysis, and two of these suffered early rethrombosis. The remaining four patients were excluded from thrombolysis by the arteriographic appearances. ^{111}In-labelled P256 Fab′ imaging can identify sites of acute arterial thrombosis and may have clinical applications in the management of peripheral vascular disease. Further studies are required to test whether the technique has a role to play in patient selection for thrombolysis.

Peripheral arterial thrombolysis is being increasingly used in the treatment of acute and subacute lower limb ischaemia with favourable results[1–3]. Its use in the treatment of chronic arterial occlusion has been less encouraging[4]. Arteriography cannot distinguish between recent and chronic occlusion and at present this aspect of patient selection depends primarily on clinical history. Despite a policy of restricting lysis to patients with a history of less than 30 days, in a number of patients there is no radiological evidence of lysis. It seems likely that in these patients the arterial occlusion is chronic and the clinical history is unreliable.

Platelet imaging using ^{111}indium oxine-labelled platelets has been previously shown to be capable of demonstrating arterial, intracardiac[5] and venous thrombi[6]. It has also been of use in the investigation of platelet deposition on arterial prosthetic grafts[7]. However, this technique requires considerable time and technical skill for cell separation and labelling. A further problem is that, owing to incomplete cell separation, there is often a substantial contamination of the platelet plug with leucocytes which, when labelled, produces a relatively high background uptake. This high background uptake reduces image contrast and necessitates long imaging times to obtain satisfactory results. It is therefore not ideally suited to widespread use as a means of detecting acute arterial thrombosis.

The present study was carried out using a recently developed immunoglobulin G_1 (IgG_1) mouse monoclonal antibody fragment specific for the glycoprotein IIb/IIIa receptor on platelets (P256 Fab′)[8]. This agent was assessed for its ability to detect arterial thrombus quickly and reliably. In addition, the extent of uptake was compared with the subsequent success of thrombolytic therapy.

Patients and methods

Seventeen patients with a history of sudden development or deterioration of lower limb ischaemia within the preceding 30 days and who were considered suitable for thrombolysis on clinical grounds were studied. All gave informed consent to participate in the study, which was approved by the Hospital Ethical Committee and the Administration of Radioactive Substances Advisory Committee.

One hundred micrograms of P256 Fab′ (Amersham International plc, Amersham, UK) was labelled with 20 MBq ^{111}indium chloride (INSIP, Amersham International plc). Before injection, 5 ml venous blood was obtained for subsequent anti-mouse antibody studies. The serum was separated and stored at −40°C until analysed. The P256 antibody preparation was given in a volume of 10 ml by slow intravenous injection. A further venous blood sample was taken after 20 min to perform estimates of platelet-associated radioactivity.

Images were recorded for 300 s per view, using a large field of view IGE 400AC γ-camera fitted with a medium energy collimator (300 keV maximum) and dual energy windows centred on both photopeaks of ^{111}In (173, 247 keV). Images were obtained after 20 min, 4–5 h, and 24 h.

Immediately after the last imaging period, the patients underwent arteriography and subsequent intra-arterial thrombolysis if this was still considered appropriate at this stage. The P256 images were not used in the selection of patients for treatment. The protocol for intra-arterial thrombolysis has previously been reported[9]. The results of the imaging technique and its comparison with arteriography and the outcome of treatment were assessed at the end of the trial. A further venous sample was obtained from seven patients 3 weeks after the study to assess any anti-mouse antibody response. All samples were assayed using an immunoenzyme procedure (ETI-Hamak, Sorin Biomedica, Salvggia, Italy).

Results

Of the 17 patients studied, 13 subsequently underwent peripheral arterial thrombolysis (four were excluded from thrombolysis because of the appearances at subsequent arteriography). In the group undergoing thrombolysis, there were six patients in whom positive P256 Fab′ antibody images were obtained and seven in whom negative images were obtained. Positive uptake was visualized as localized regions of high uptake corresponding to an occluded arterial segment on arteriography (*Figure 1*). This was seen as early as 5 h after injection with, in some cases, improved definition after 24 h.

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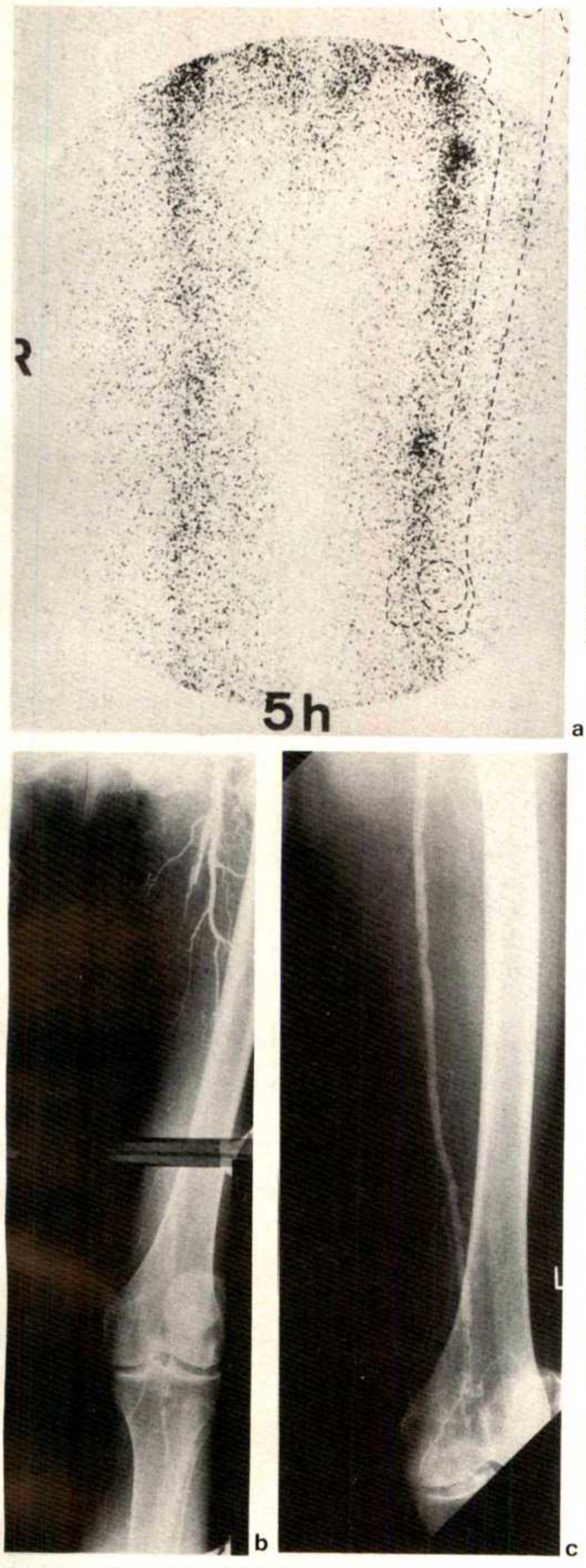

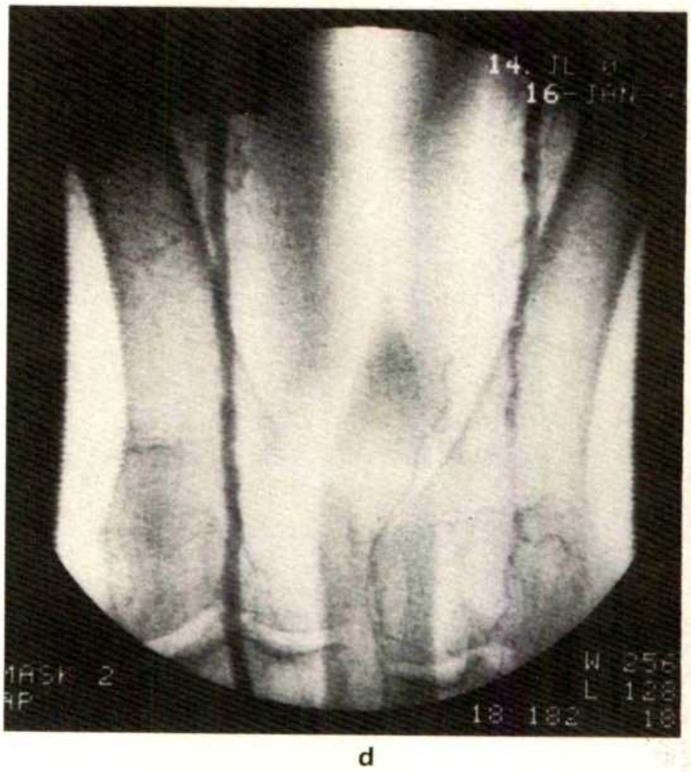

Figure 1 **a** *Image obtained after 5 h demonstrates discrete uptake foci in the proximal and distal left superficial femoral artery.* **b, c** *Subsequent arteriography confirms an occlusion in this artery, and suggests that the occlusion (thrombus) continues into the popliteal artery.* **d** *Thrombolysis readily lyses the thrombus but only to the extent shown on the P256 Fab′ image. Two major collaterals perfuse the lower limb and have remained patent after 3 months*

Table 1 *Details of scan result, treatment and outcome in 17 patients*

Patient no.	Duration of history (days)	Scan result	Initial lysis	Outcome
Undergoing thrombolysis				
1	14	Positive	Yes	Rethrombosed
2	14	Positive	Yes	Successful
3	7	Positive	Yes	Successful
4	14	Positive	Yes	Successful
5	5	Positive	Yes	Successful
6	9	Positive	Yes	Rethrombosed
7	28	Negative	No	Failed
8	21	Negative	Yes	Rethrombosed
9	28	Negative	Yes	Successful
10	10	Negative	Yes	Rethrombosed
11	16	Negative	No	Failed
12	3	Negative	Yes	Successful
13	21	Negative	No	Failed
Excluded from thrombolysis				
14	28	Positive	Treated with angioplasty	
15	4	Positive	Iliac aneurysms (aorto-bifemoral graft)	
16	2	Negative	Two ipsilateral occlusions	
17	14	Negative	Two ipsilateral occlusions	

On commencing thrombolysis in the six patients with positive images, there was rapid lysis of thrombus in the arterial segment corresponding to the site of high uptake. In four patients this resulted in restoration of arterial patency which was maintained at 30 days. In the remaining two patients severe arterial disease below the thrombosed segment was revealed. In neither case was this amenable to angioplasty or bypass and in both cases the lack of run-off resulted in early rethrombosis (*Table 1*).

The results of thrombolysis in the seven patients with negative images were less good. In only two patients was thrombolysis successful with arterial patency maintained at 30 days. In three patients there was no significant thrombus lysis at all, and in the final two patients lysis occurred but was incomplete and rapid rethrombosis occurred.

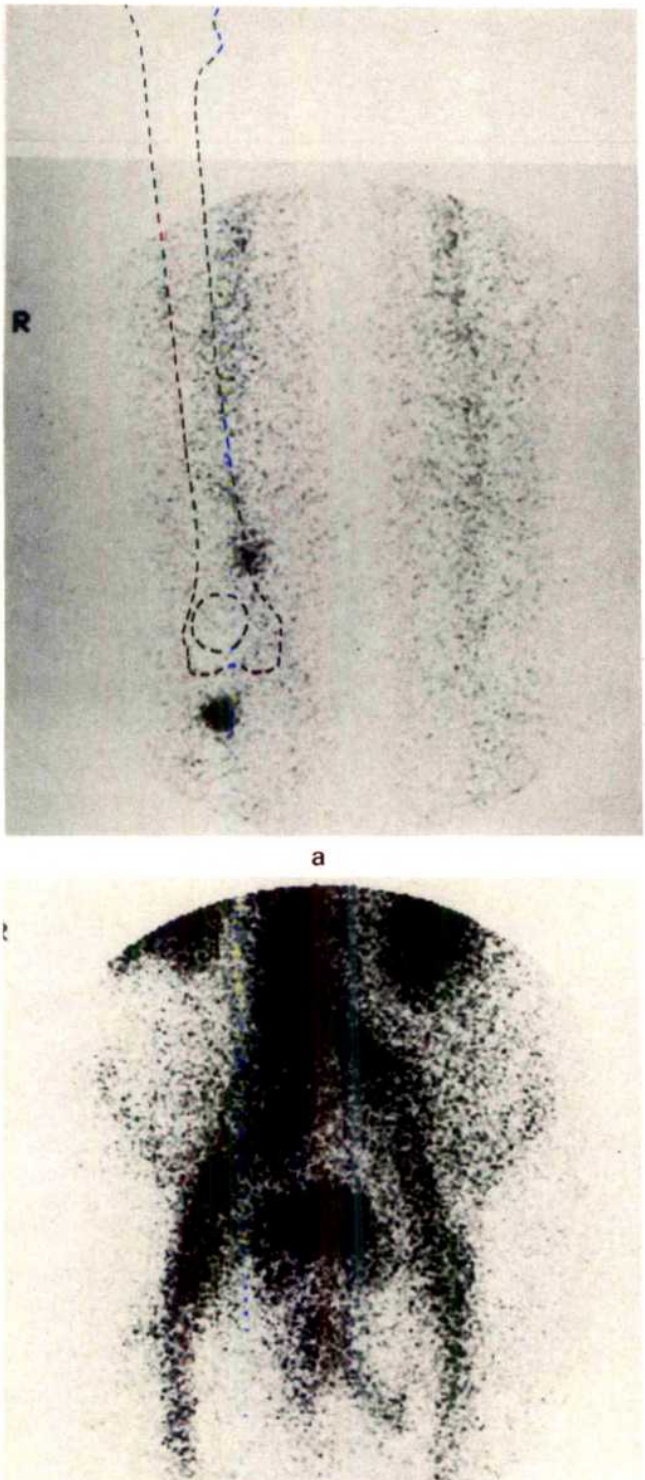

Figure 2 **a** *Image obtained after 5 h reveals two foci of increased uptake in the lower right superficial femoral artery.* **b** *Pelvic views show increased uptake in the right and left common iliac arteries and right femoral arteries. Subsequent ultrasonography confirmed bilateral iliac aneurysms. Arterial reconstruction was performed and the emboli were extracted*

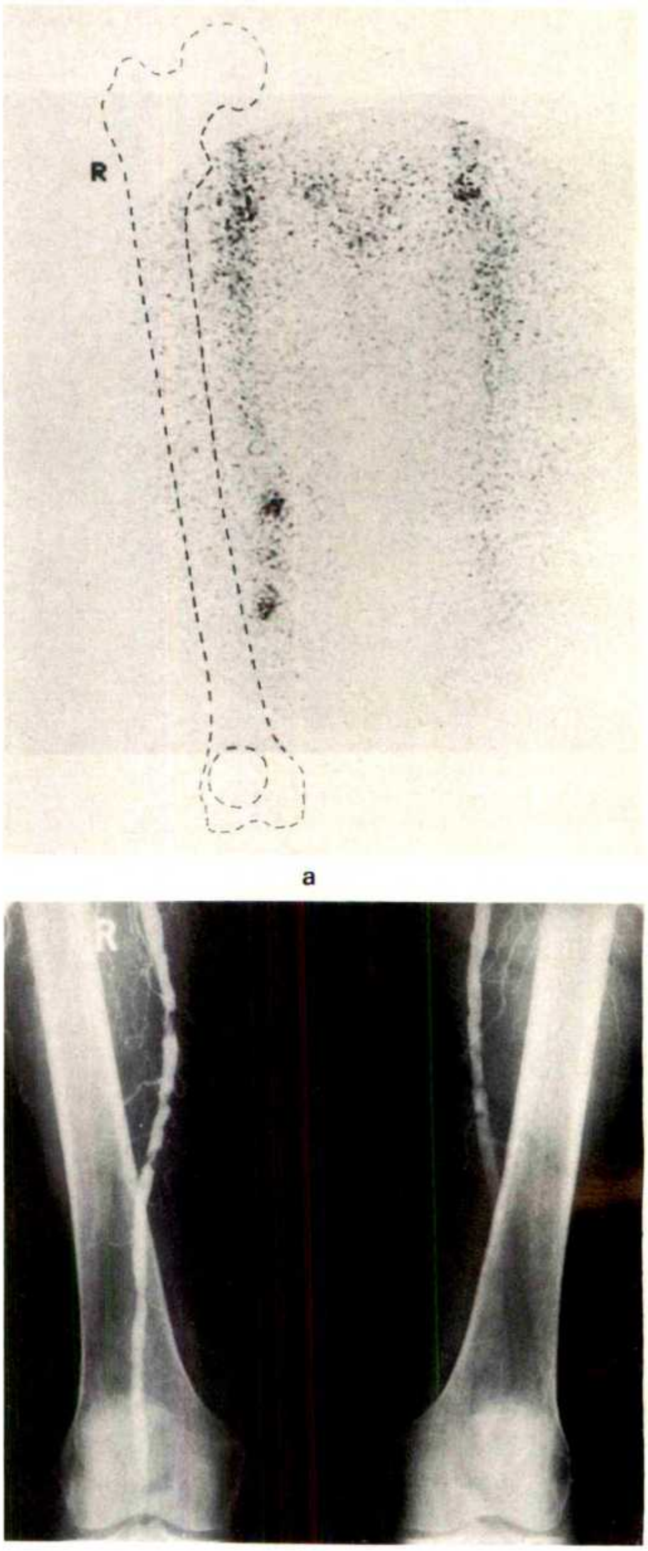

Figure 3 **a** *Image after 5 h demonstrating two highly positive foci separated by a less distinct focus.* **b** *Subsequent arteriography reveals that these foci were at sites of 90 and 75 per cent stenoses respectively*

Four patients were excluded from thrombolysis. Two had both iliac and superficial femoral artery occlusions on the same side, one of which was almost certainly chronic, and therefore it was felt that the likelihood of a successful outcome from thrombolysis was significantly reduced; surgical reconstruction was carried out instead. The other two patients were particularly interesting. In the first, bilateral regions of high uptake were seen in the pelvis together with an additional focus of high uptake corresponding to the tibioperoneal trunk (*Figure 2*). Ultrasonography revealed the presence of clinically occult bilateral iliac aneurysms and it seems likely that distal embolization from these was responsible for the distal occlusion. An aortobifemoral graft with ligation of the iliac aneurysms was performed with a successful outcome. The final patient had two areas of high uptake in the superficial femoral artery (*Figure 3*); arteriography revealed these to correspond to 75 and 90 per cent stenoses respectively. These were dilated by balloon angioplasty.

Assay of the blood samples taken 20 min after injection showed approximately 80 per cent of the blood radioactivity to be associated with circulating platelets[10]. Assay of the blood from seven patients taken 3 weeks after the study showed no evidence of production of human anti-mouse antibody. A longer term follow-up is being undertaken to determine whether a later response occurs. No side-effects were noted in any of the patients.

Discussion

Peripheral arterial thrombolysis is potentially of great benefit to patients with peripheral arterial thrombosis, many of whom are unsuitable for reconstructive surgery. It is, however, associated with a small but significant risk of death due principally to haemorrhagic stroke and other bleeding complications[11]. Accurate patient selection is therefore important. The age of an arterial thrombus is a significant factor in determining whether peripheral arterial thrombolysis will be successful. Lesions of up to 30 days quite commonly undergo successful lysis. If older lesions are treated the success rate fails and the time taken to achieve lysis (and hence the complication rate) increases. Therefore the ability to differentiate between a truly chronic arterial occlusion and an acute or subacute arterial thrombus has important clinical implications.

The previously described technique of imaging arterial thrombus using ^{111}indium oxine-labelled platelets produces images of only moderate quality and is too slow and technically demanding to be used as a routine diagnostic tool before peripheral arterial thrombolysis. The technique described in this study appears to overcome these difficulties with high quality images being obtained as early as 4 h after a single intravenous injection.

In this pilot study we have shown that imaging with ^{111}In-labelled P256 Fab′ identifies regions of high uptake that were in every case successfully lysed and therefore can be presumed to correspond to recent thrombus. Two problems were encountered which may limit future application of this technique. Firstly, despite successful lysis the arterial segment may still rethrombose because of inadequate run-off. Retrospective review of the P256 Fab′ images and arteriograms of the two patients in which this occurred suggests that in future it may be possible to predict these cases. In both patients the region of high uptake on the P256 Fab′ image was localized to the popliteal region but on arteriography there was no evidence of patent vessels distal to the knee on delayed films. It is possible that these appearances predict the presence of a localized thrombosis proximal to more chronic disease. Secondly, although the technique appears to be fairly specific for predicting thrombus lysis, it is clearly not sensitive since two of the seven patients with negative scans had successful lysis.

An interesting finding in this study has been the positive P256 Fab′ image obtained in a patient with arterial stenoses as opposed to arterial occlusion. This suggests that platelet deposition was occurring at the sites of these stenoses and raises the possibility that in this patient a stenosis was identified which may ultimately have occluded. We are currently undertaking further studies in patients with arterial stenoses that on current criteria do not justify treatment, to explore whether this technique can identify a subgroup of patients with thrombogenic stenoses in whom acute arterial thrombosis is imminent.

This study has demonstrated that *in vivo* platelet labelling using ^{111}In-labelled P256 Fab′ may be used to identify arterial thrombi. The technique is an advance on current platelet labelling techniques using ^{111}indium oxine. The small numbers in this pilot study prevent any conclusions from being made on the ability of the technique to predict successful thrombolysis. However, we believe that the results are sufficiently encouraging to merit further study, and that in the future P256 Fab′ imaging may be a useful investigative tool for assessing the age of arterial thrombi and hence the likely outcome of thrombolysis.

Acknowledgements

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References

1. Risius B, Groar RA, Geisibger MA *et al.* Recombinant human tissue type plasminogen activator for thrombolysis in peripheral arteries and bypass grafts. *Radiology* 1986; **160**: 183–8.
2. McNamara TO, Fischer JA. Thrombolysis of peripheral arterial and graft occlusions: improved results using high dose urokinase. *Am J Radiol* 1985; **144**: 769–75.
3. Walker WJ, Giddings AEB. A protocol for safe treatment of acute lower limb ischaemia with intra-arterial streptokinase and surgery. *Br J Surg* 1988; **75**: 1189–92.
4. Van Breda A, Katzen BT. Radiological aspects of intra-arterial thrombolytic therapy. In: Comerota AJ, ed. *Thrombolytic Therapy*. Orlando: Grune and Stratton, 1988: 99–124.
5. Davis HH, Siegel BA, Joist JH *et al.* Scintigraphic detection of atherosclerotic lesions and venous thrombi in man by indium-111-labelled autologous platelets. *Lancet* 1978; **i**: 1185–7.
6. Seebold JE, Conrad GR, Kimball DA, Ponto JA, Bricker JA. Pitfalls in establishing the diagnosis of deep venous thrombophlebitis by indium-111 platelet scintigraphy. *J Nucl Med* 1988; **29**: 1169–80.
7. Goldman M, Norcott HC, Hawker RJ, Hail C, Drole Z, McCollum CN. Femoro-popliteal bypass grafts – an isotope technique allowing *in vivo* comparison of thrombogenicity. *Br J Surg* 1982; **69**: 380–2.
8. Lavender JP, Stuttle AWJ, Peters AM, Harrison RC, Murphy GJ. Imaging venous thrombi in the post-operative patient using indium-111 P256 Fab′ monoclonal antibody. *Nucl Med Commun* 1989; **10**: 375.
9. Berridge DC, Gregson RHS, Hopkinson BR, Makin GS. Intra-arterial thrombolysis using recombinant tissue plasminogen activator (r-TPA): the optimal agent, at the optimal dose? *Eur J Vasc Surg* 1989; **3**: 327–32.
10. Frier M, Perkins A, Berridge DC *et al.* Characterisation and clinical use of P256 Fab′ platelet specific monoclonal antibody in the detection of arterial thrombosis. In: Schmidt HAE, Chambon J, eds. *Nuclear Medicine Quantitative Analysis in Imaging and Function*. Stuttgart: Schauttauer, 1990: 288–90.
11. Berridge DC, Makin GS, Hopkinson BR. Local low-dose thrombolytic therapy: the risk of stroke or major haemorrhage. *Br J Surg* 1989; **76**: 1230–33.

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Retrograde femoral angioplasty: a new technique

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Percutaneous transluminal angioplasty cannot be used for lesions of the superficial femoral artery when the origin of the vessel is occluded. A new technique, retrograde femoral angioplasty, is described in which angioplasty is performed from below via the exposed popliteal artery. In four out of six patients retrograde femoral angioplasty was successfully completed, and three of the four vessels remain patent up to 1 year later. The method provides an alternative to the femoropopliteal bypass graft in some patients.

Percutaneous transluminal angioplasty (PTA) is now a well established technique for the treatment of stenotic or occlusive lesions of the arterial tree. In claudicants PTA gives results comparable to surgery[1], although for patients with limb-threatening ischaemia results seem less good and less durable[2]. PTA of the superficial femoral artery requires the passage of a guidewire down the artery. This is done via a needle puncture of the common femoral (or sometimes of the superficial femoral) artery in an antegrade direction using the Seldinger technique. The guidewire is passed through the stenosis or occluded segment and its position verified by fluoroscopy. A dilator is then passed over the guidewire to facilitate the insertion of an introducing sheath and a balloon catheter. If the guidewire will not negotiate an occluded lesion then a channel for the wire may be formed by a laser fibre[3]. After satisfactory laser recanalization, an angioplasty balloon catheter replaces the laser fibre and balloon dilatation is performed.

Occlusion or tight stenosis at the origin of the superficial femoral artery (*Figure 1a*) renders antegrade insertion of a guidewire impossible; the wire usually passes preferentially into the profunda femoris artery. Furthermore, when the standard antegrade Seldinger technique is used via the groin, the common femoral artery itself cannot be dilated. PTA carries a number of well recognized, if infrequent, complications of which haemorrhage is the most common[4].

This early report introduces retrograde femoral angioplasty, a new technique which we believe may overcome some of these problems and which seems worthy of further evaluation.

Methods

Retrograde femoral angioplasty is suitable for patients with stenotic or occlusive lesions at the origin of the superficial femoral artery in whom there is distal reconstitution of the vessel in the popliteal fossa. The procedure may be carried out under local anaesthesia in either the operating theatre or X-ray department. The technique requires exposure of the popliteal artery below the adductor hiatus. The artery can be approached either from above or below the knee, depending on how distally the vessel reconstitutes.

The leg is prepared in the usual manner and is flexed over a radiolucent pad placed behind the knee. The common femoral artery is marked with a radio-opaque marker placed on the skin over the pulse. After infiltration with local anaesthetic, a 5–10 cm incision is made on the medial aspect of the leg at the chosen level along the line of the popliteal artery, taking care to avoid the long saphenous vein. The artery is exposed and punctured under direct vision using a 6 Fr arterial needle through which a guidewire can be passed up towards the groin. An introducing sheath is then inserted. When a guidewire has been passed to the level of the radio-opaque groin marker and its position confirmed on fluoroscopy, a balloon catheter is inserted (*Figure 1b*). Dilatation of the superficial femoral artery from above downwards is then completed (*Figure 1c*).

If the guidewire fails to negotiate an occluded segment then, as is our practice with the standard antegrade approach, we use a YAG laser with sapphire tip to recanalize the arterial lumen before balloon angioplasty. Following the procedure the artery is repaired using a single 6/0 polypropylene suture and the wound closed over a suction drain. The patient remains in hospital overnight but may be discharged the following day after removal of the drain.

Results

Only six patients have undergone this procedure so far, four with claudication and two with rest pain. Follow-up is from 10 to 16 months.

Two patients had a retrograde balloon angioplasty with immediate successful outcome and their arteries remain patent both on clinical and Doppler ultrasound examination at 10 and 16 months, respectively. The remaining four patients underwent laser-assisted retrograde balloon angioplasty. Two had immediate success, but while one patient with rest pain still has a patent artery and is symptom-free at 15 months, the other patient reoccluded his artery 6 weeks after dilatation and underwent a subsequent successful bypass procedure.

In the final two patients recanalization was unsuccessful. In each case the artery was perforated by the laser fibre but without bleeding or haematoma formation or any other ill effect. Both these patients had heavy calcification of the vessel visible on plain radiograph. Thus of the six patients, three have had an excellent result lasting 10, 15 and 16 months respectively, one has reoccluded at 6 weeks and two have failed to benefit.

Discussion

Angioplasty in the management of patients with peripheral vascular disease has been shown to be a useful and successful technique[1,2]. For patients with stenotic or occlusive lesions at the origin of the superficial femoral artery, failure to pass the guidewire safely has meant that femoropopliteal bypass may be required. Retrograde femoral angioplasty may offer an acceptable alternative.

The technique has the disadvantage of requiring open exposure of the popliteal artery, but this can be done under local anaesthesia and in the X-ray department. Although percutaneous puncture of the popliteal artery has been attempted, it is difficult and is certainly not an established technique. Direct exposure of the popliteal artery, especially in its upper portion, is simple for an experienced vascular surgeon and has the advantage that repair of the puncture site by a single suture precludes any haemorrhage following the procedure. Accidental perforation of the vessel distal to an occlusion by the guidewire or laser fibre using the retrograde technique results in less extravasation of blood into the tissues than perforation using the antegrade approach. Control of the vessel by slings prevents emboli dislodged at the time of angioplasty from passing into the distal arterial tree. The retrograde approach carries the further advantage that a diseased common femoral artery can be dilated after the superficial femoral artery has been rendered patent; this is not possible using the antegrade approach via the groin.

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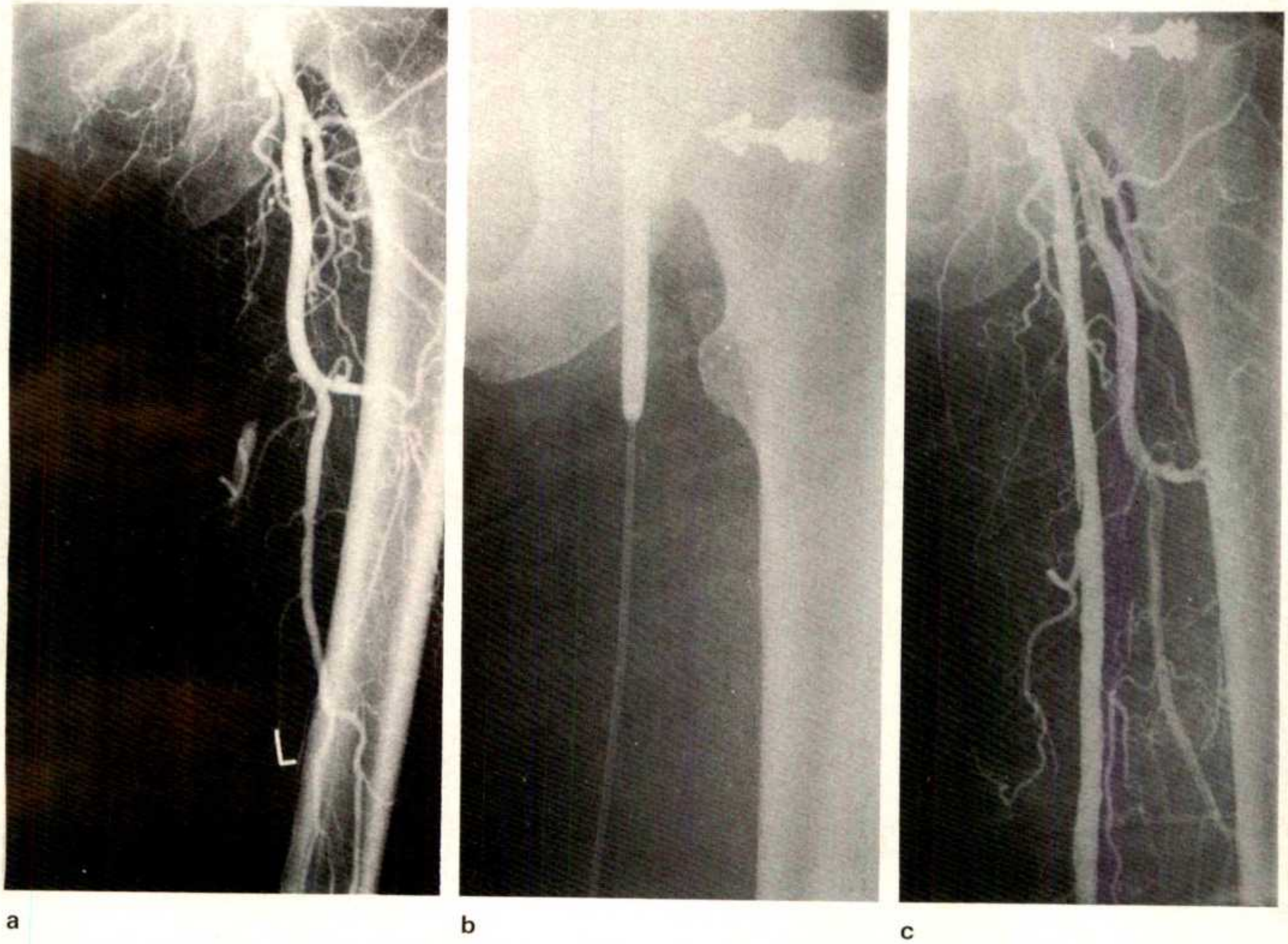

Figure 1 **a** *Arteriogram showing occlusion of the superficial femoral artery at its origin;* **b** *plain radiograph showing the angioplasty balloon inserted from below and inflated at the origin of the superficial femoral artery. The skin marker is at the level of the common femoral artery;* **c** *angiogram after retrograde angioplasty*

This retrograde method requires more patients to be treated and followed up over longer periods of time before it can be fully assessed. Nevertheless it seems to carry few complications and does not prevent further vascular surgical intervention. We believe that retrograde femoral angioplasty may offer an acceptable treatment for patients with stenotic or occlusive disease at the origin of the superficial femoral artery.

References

1. Wilson SE, Wolf GL, Cross AP. Percutaneous transluminal angioplasty versus operation for peripheral vascular arteriosclerosis. *J Vasc Surg* 1989; **9**: 1–9.
2. Blair JM, Gewertz BL, Moosa H, Chien Thai LU, Sarins CK. Percutaneous transluminal angioplasty versus surgery for limb threatening ischaemia. *J Vasc Surg* 1989; **9**: 698–703.
3. White RA, White GH. Laser thermal probe recanalization of occluded arteries. *J Vasc Surg* 1989; **9**: 598–608.
4. Weibull H, Bergqvist D, Jonsson K, Karlsson S, Takolander R. Complications following percutaneous transluminal angioplasty. *J Vasc Surg* 1987; **5**: 681–6.

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Management of critical upper limb ischaemia long after irradiation injury of the subclavian and axillary arteries

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Radiation injury to arteries supplying the upper limb following treatment for carcinoma of the breast has been the subject of occasional case reports[1–7]. Damage to subclavian and axillary arteries can eventually result in critical ischaemia endangering the upper limb. The surgical options available in such cases are illustrated by recent experience in the management of four patients, all of whom were operated on by the second author.

Case reports

Case 1

A 45-year-old woman presented with an acute critically ischaemic right hand which was preceded by a 5-month history of claudication in the right arm. Six years previously she had undergone a simple mastectomy for carcinoma followed by radiotherapy. On examination the fingers of her right hand were pale, cold and tender. The right brachial and radial pulses were absent and blood pressure could not be recorded in the arm.

Arch aortography was normal except for the distal right axillary artery, a 1-cm segment of which was severely stenosed. Dilatation by percutaneous transluminal angioplasty restored the radial pulse to normal, but ischaemic symptoms returned 1 year later. Angiography revealed an occluded axillary–brachial artery segment, and a further radiological attempt at recanalization not only failed but rendered the forearm and hand critically ischaemic. Urgent operative intervention took the form of an axillobrachial reversed vein bypass graft, restoring distal pulses and skin circulation which have been sustained for 5 years.

Case 2

A 62-year-old woman presented with two pallid and painful fingers of the left hand preceded by a 3-year history of claudication in the left arm. Carcinoma of the left breast, diagnosed 11 years previously, had been treated by radical mastectomy and radiotherapy. Seven years later a similar diagnosis in the opposite breast led to simple mastectomy. On examination she had a left infraclavicular bruit, a poor brachial pulse and an absent left radial pulse. The skin over the irradiated area was thin and had scattered telangiectasiae.

Doppler ultrasound examination of the right brachial artery revealed a high amplitude triphasic pulse waveform with an occlusion pressure of 185 mmHg; on the left side it was low-amplitude and monophasic with an occlusion pressure of 120 mmHg. Arch aortography revealed critical stenosis of a 2-cm segment of the second part of the left subclavian artery. All other vessels in the study were normal.

A supraclavicular incision was employed, but the absence of normal tissue planes made dissection and identification of anatomical structures difficult and periarterial fibrosis rendered arterial control hazardous. The diseased arterial segment was, however, replaced by an interposed 6-mm polytetrafluoroethylene (GORE-TEX®, W. L. Gore and Associates Ltd, Woking, UK) graft. Normal arm pulses, a rise in left arm pressure to 175 mmHg and a normal pulse waveform were corroborated by immediate and continued relief of symptoms.

Case 3

A 74-year-old woman had been treated for carcinoma of the right breast by radical mastectomy and radiotherapy 33 years previously (*Figure 1a*). She complained of exercise-induced pain in the right arm for 2 months before developing gangrene of the right index finger and tip of the right thumb, apparently precipitated by minor blunt injury 6 weeks previously (*Figure 1b*). The right hand was pale and cool, and pulses throughout the right arm were impalpable. The skin in the irradiated area was scarred and covered by numerous telangiectasiae.

Brachial artery occlusion pressures were recorded at 170 mmHg on the left and 40 mmHg on the right. Correspondingly, pulse waveforms on the left were of high amplitude and triphasic in character, whereas on the right they were of very low amplitude and monophasic (*Figure 2*). Angiography showed complete occlusion of the right subclavian and axillary arteries with poorly developed collaterals filling a small calibre brachial artery distally (*Figure 2*). Areas of irradiation necrosis were observed in the right scapula, humerus and upper ribs, and the right lung field showed evidence of pulmonary fibrosis.

A reversed long saphenous vein graft was used to construct a right common carotid–brachial artery bypass; it was tunnelled deep to

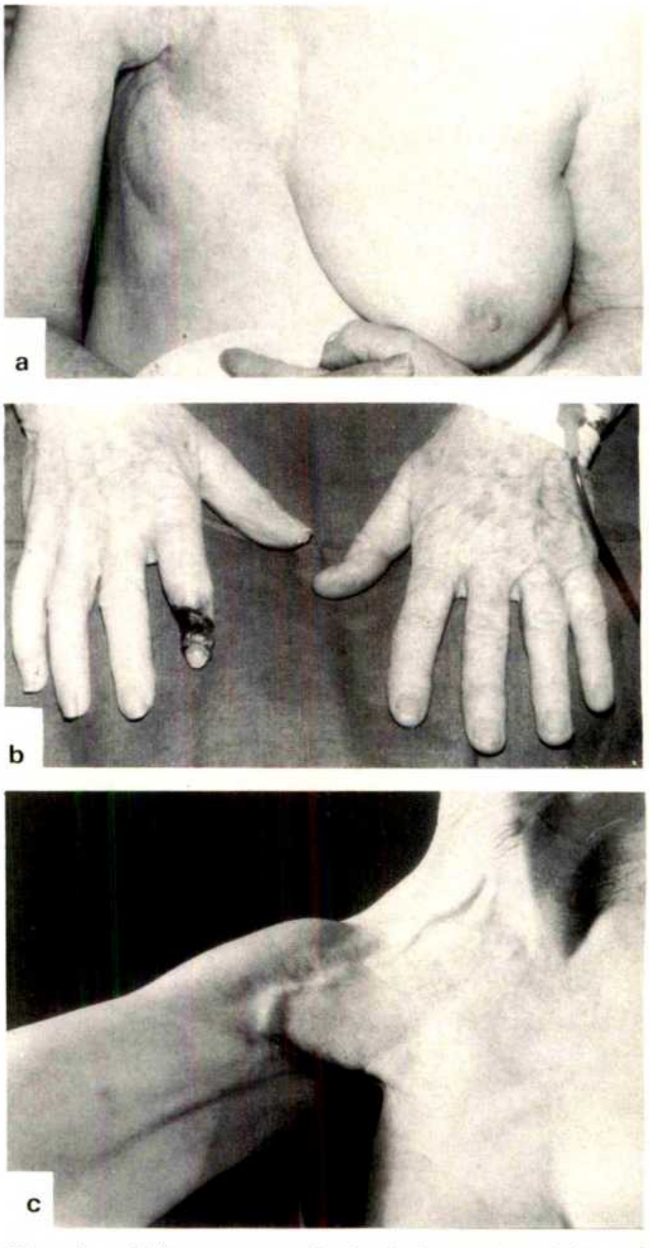

Figure 1 **a** *Right mastectomy. Postirradiation scarring of skin with multiple telangiectasiae;* **b** *marked pallor of right hand (normal circulation in left) with gangrene of index finger and tip of thumb;* **c** *carotid–brachial vein bypass graft clearly visible as it traverses a subcutaneous extra-anatomical path*

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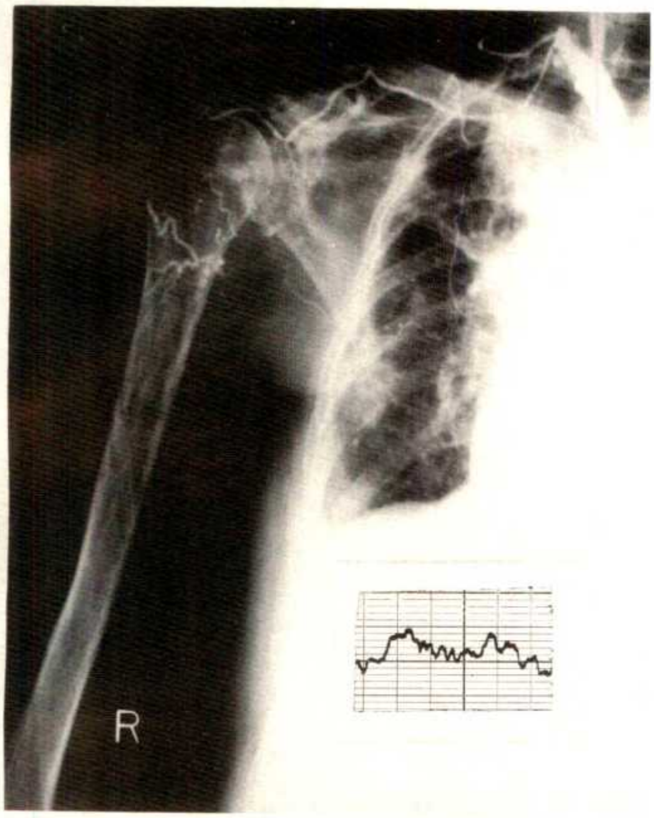

Figure 2 *Arch aortography: occluded right subclavian, axillary and proximal brachial artery, poorly formed collateral circulation. Note patchy irradiation necrosis of scapula, humerus and upper ribs as well as lung fibrosis. Inset: low-amplitude monophasic Doppler brachial pulse waveform*

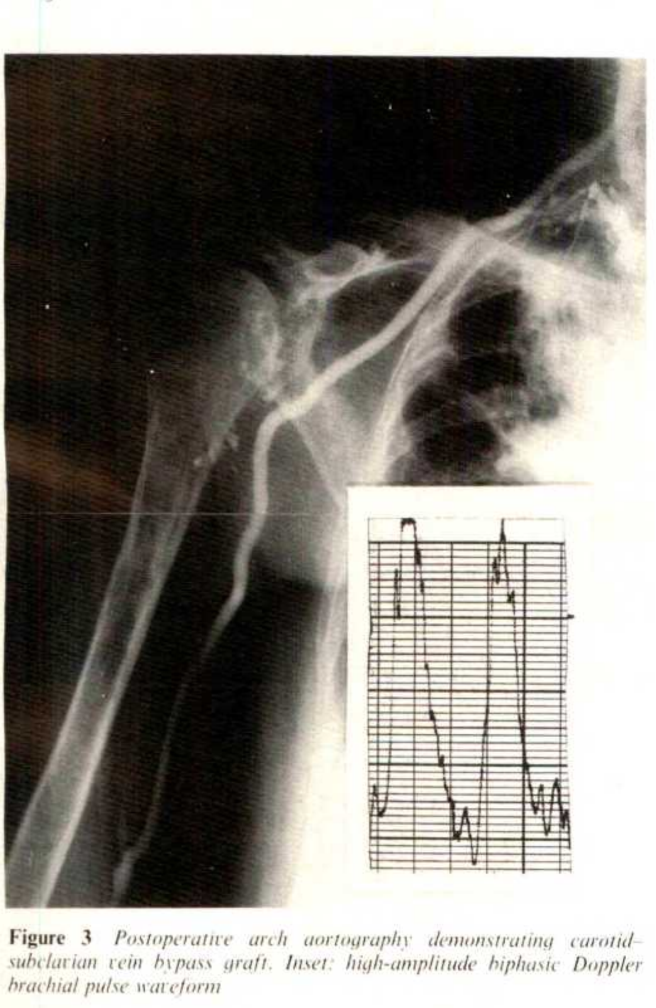

Figure 3 *Postoperative arch aortography demonstrating carotid–subclavian vein bypass graft. Inset: high-amplitude biphasic Doppler brachial pulse waveform*

the sternomastoid and subcutaneously over the clavicle, pectoralis major and medial aspect of the upper arm (*Figure 1c*). The index finger and tip of thumb were amputated.

The tissues healed quickly and all symptoms cleared. Brachial artery occlusion pressures in each arm were recorded at 190 mmHg with high-amplitude biphasic pulse waveforms (*Figure 3*). Angiography confirmed an entirely satisfactory carotid–brachial bypass graft (*Figure 3*), and 3 years later the patent extra-anatomical graft is clearly visible (*Figure 1c*).

Case 4

A 60-year-old woman presented with an acute, critically ischaemic right hand. Carcinoma of the right breast 17 years previously had been treated by simple mastectomy and radiotherapy. On examination the right hand and forearm were pale, cool and tender, and pulses in the right arm were impalpable. Sensation in a glove distribution was diminished and power in the hand and at the wrist was absent. Systolic blood pressure in the left arm was 190 mmHg but was unrecordable in the right.

Angiography showed that the right subclavian artery was occluded from its origin, the axillary artery was stenosed, and the distal brachial artery was patent though attenuated, being filled by poorly established collaterals.

A reversed long saphenous vein graft was used to construct an extra-anatomical right common carotid–brachial artery bypass and tunnelled in the same manner as for Case 3. A bounding right radial pulse with good skin circulation was restored, as were normal sensation and power in the forearm and hand.

Discussion

Irradiation-induced injury of the subclavian and axillary arteries is uncommon and usually follows radiotherapy for breast carcinoma. The vast majority of patients who undergo radiotherapy for malignant breast disease never develop symptomatic arterial disease, possibly because many do not survive long enough to do so. It is possible that symptoms affecting the upper limbs, as a consequence of mastectomy, tumour spread or radiotherapy, may conceal features of arterial insufficiency.

The pathogenesis of irradiation-induced occlusive disease in large arteries, such as the subclavian and axillary, involves three processes[8], namely endothelial injury and disruption of the internal elastic lamina followed by intimal fibrosis and plaque formation, occlusion of the vasa vasorum by proliferation and hyaline thickening of the intima which in turn causes fibrosis of the media, and, lastly, periarterial fibrosis which brings about extrinsic constriction of the artery.

Four distinct patterns of irradiation-induced arterial disease have been described[2,8–10]. The first is unusual and is represented by dramatic early arterial wall necrosis causing arterial rupture, which in neck vessels is potentially fatal. In the second type, mural thrombosis in the arterial segment at the site of irradiation usually presents as a symptomatic entity within 5 years. In the third, fibrotic occlusion of the irradiated artery may lead to the development of symptoms within 10 years. The fourth group manifests itself more than 20 years after radiotherapy with symptoms initiated by periarterial fibrosis and 'accelerated atherosclerosis'.

In subclavian arteries it may be difficult to distinguish, either angiographically or histologically, between arterial damage caused by irradiation and atherosclerosis. In the cases described, the axillary and subclavian arterial lesions were confined to the irradiated field alone and were quite easily differentiated from atherosclerotic disease which has a relatively ubiquitous distribution. Several features do implicate radiotherapy; namely irradiation within the boundaries of a supraclavicular portal, the involvement of vessels only within that field, the occurrence of such localized pathology in relatively young people, and the density of periarterial fibrosis not commonly associated with atherosclerosis of these vessels[2,9,10].

As the critical dose of irradiation sufficient to produce an arterial lesion is unknown[7], it must be assumed that there is considerable individual variation in sensitivity to radiotherapy.

Irradiation-induced arterial injury is reported to be exacerbated by pre-existing hypertension[11,12] and hypercholesterolaemia[13]. Hypertension was noted at presentation in Cases 2, 3 and 4, but hypercholesterolaemia was not demonstrated in any of the cases reported here.

The extent of irradiation injury of the arterial system supplying the upper limb will dictate management. A short stenosed arterial segment may appear amenable to percutaneous transluminal angioplasty[14], but, as this technique relies on successful dilatation of the entire thickness of the arterial wall, it is, on theoretical grounds, less likely to succeed if transmural or periarterial fibrosis is present.

A short segment of occluded artery may be approached through a single incision and bypassed by means of an anatomically sited graft, as in Case 2. Against this, the presence of periarterial fibrosis and loss of normal tissue planes make dissection technically difficult and even hazardous, and irradiated skin may be slow to heal. Irradiated host tissue, being fibrotic and poorly nourished, represents an inhospitable milieu wherein a vein graft is less likely to survive or indeed maintain its calibre and eventual patency. Synthetic material requires a degree of bonding by the surrounding tissues, but it is not as immediately dependent as a vein graft might be on the state of nutrition of these tissues.

Extra-anatomical bypass grafts, which can be routed through relatively healthy tissues, as in Cases 3 and 4, are reserved for more extensive disease. The two potential inflow arteries for this purpose are the ipsilateral common carotid and the contralateral subclavian, of which the former is the vessel of choice. A graft from the contralateral subclavian artery may either be routed subcutaneously over the anterior chest wall (where it is unsightly) or tunnelled deep to the sternomastoid muscles and anterior to each carotid sheath. However, this path may render the graft vulnerable to occlusion at extremes of neck movement.

It was suggested that an ipsilateral carotid–subclavian bypass carries a risk of 'carotid steal'[15], in which cerebral blood flow is siphoned down the carotid system to produce neurological symptoms. This concern was assuaged by the findings of an elegant study which showed this operation to be haemodynamically valid and acceptable as long as the common carotid artery is not stenosed proximally[16]. No symptoms of such steal were observed in the two patients in whom the carotid–brachial bypass technique was employed. On the contrary, this reconstructive approach proved effective and, given the superficial and undulating path employed, a vein graft seemed to give the best chance of long-term patency.

Radiotherapy for breast carcinoma is an uncommon but eminently treatable cause of critical upper limb ischaemia. Patients should be referred to a specialist vascular unit for appropriate reconstructive limb salvage surgery. The therapeutic options are varied, but in our opinion the construction of an extra-anatomical carotid–brachial vein bypass for extensive occlusions is to be recommended.

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References

1. Budin JA, Casarella WS, Harisiadis L. Subclavian artery occlusion following radiotherapy for carcinoma of the breast. *Radiology* 1976; **118**: 169–73.
2. Butler MS, Lane RHS, Webster JHH. Irradiation injury to large arteries. *Br J Surg* 1980; **67**: 341–3.
3. Hughes WF, Carson CL, Laffaye HA. Subclavian artery occlusion 42 years after mastectomy and radiotherapy. *Am J Surg* 1984; **147**: 698–700.
4. Loeffler RK. Subclavian artery occlusion following radiation therapy. *Invest Radiol* 1975; **10**: 391–3.
5. Mavor GE, Kasenally AT, Harper DR, Woodruff PWH. Thrombosis of the subclavian-axillary artery following radiotherapy for carcinoma of the breast. *Br J Surg* 1973; **60**: 983–5.
6. Kretschmer G, Niederle B, Potterauer P, Waneck R. Irradiation-induced changes in the subclavian and axillary arteries after radiotherapy for carcinoma of the breast. *Surgery* 1986; **99**: 658–63.
7. Bergqvist D, Jonsson K, Nilsson M, Takolander R. Treatment of arterial lesions after radiation therapy. *Surg Gynecol Obstet* 1987; **165**: 116–20.
8. Johnson AG, Lane B, Harding-Rains AJ *et al.* Large artery damage after X-irradiation. *Br J Radiol* 1969; **42**: 937–9.
9. Benson EP. Radiation injury to large arteries. *Radiology* 1973; **106**: 195–7.
10. McCready RA, Hyde GL, Bivins BA *et al.* Radiation-induced arterial injuries. *Surgery* 1983; **93**: 306–12.
11. Asscher AW, Wilson C, Anson SG. Sensitization of blood vessels to hypertensive damage by X-radiation. *Lancet* 1961; **i**: 580–3.
12. McMichael J. Reorientations in hypertensive disorders. *Br Med J* 1961; **ii**: 1310–14.
13. Kirkpatrick JB. Pathogenesis of foam cell lesions in irradiated arteries. *Am J Pathol* 1967; **50**: 291–301.
14. Gunthaner D, Schmitz L. Percutaneous transluminal angioplasty of radiation-induced arterial stenosis. *Radiology* 1982; **144**: 77–8.
15. Harper JA, Golding AL, Mazzei EA, Cannon JA. An experimental hemodynamic study of the subclavian steal syndrome. *Surg Gynecol Obstet* 1967; **124**: 1212–18.
16. Lord RSA, Ehrenfeld WK. Carotid-subclavian bypass: a haemodynamic study. *Surgery* 1969; **66**: 521–6.

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Objective assessment of high ligation without stripping the long saphenous vein

Non-invasive methods of venous assessment were used to assess the procedure of high ligation plus multiple avulsion of varicosities for the treatment of varicose veins in 54 limbs. Duplex scanning before operation confirmed saphenofemoral incompetence and excluded short saphenous incompetence. After operation it revealed that in two limbs the saphenofemoral junction was still patent and incompetent. In the 52 limbs in which the junction had been ligated there was persistent reflux down the long saphenous vein in 24 cases. In only two limbs was this attributable to mid-thigh perforating veins. Photoplethysmography was also performed before and after operation and the venous refilling time measured. Improvement in refilling time produced by application of above knee tourniquets before operation was measured (predicted improvement) and the change in refilling time after operation was also recorded (observed improvement). There was a statistically significant correlation between observed improvement and predicted improvement in refilling times in the limbs with no reflux in the long saphenous vein after operation (Pearson's correlation coefficient, $r=0{\cdot}6$, $P<0{\cdot}001$). There was no correlation between predicted and observed refilling times in the limbs with persisting reflux in the long saphenous vein after operation. In conclusion, this operation fails to control functionally significant reflux within the long saphenous vein in a high proportion of cases.

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Recurrence of symptoms after surgery for varicose veins is common[1]. Numerous studies have been performed to identify reasons for this high recurrence rate and the most common cause cited is an inadequate primary operation[2–5] with failure to perform a flush saphenofemoral ligation, meticulous ligation of all tributaries and ligation of perforating veins. There is controversy over the necessity for stripping the long saphenous vein. Studies comparing the results of stripping with results obtained by retrograde sclerotherapy or with multiple avulsions of distal varicosities have been contradictory[6–10], although most have concluded that stripping the long saphenous vein produces better immediate results and leads to a lower recurrence rate of symptoms with time. This possible advantage must be weighed against the greater morbidity associated with stripping the vein; bleeding, pain and wound infection may cause a longer hospital stay and a longer period of convalescence, considerations of economic importance. If stripping the vein is not performed, varicose vein surgery is more suitable as a day-case procedure. There is also an increased incidence of nerve damage associated with stripping[11–13], which is often of concern to patients, particularly if the operation was undertaken principally for cosmetic reasons. Finally, the long saphenous vein remains the most successful graft available for both arterial and venous reconstruction and it should not be discarded needlessly.

The numerous studies performed to determine the necessity for stripping the long saphenous vein have all relied on clinical examination and patient opinion. Symptoms such as swelling and aching are recorded before and after operation and, similarly, clinical examination, assessing severity and site of varicosities, oedema and skin changes, is performed by an observer before and after surgery, often with the help of photographs. These criteria are far from precise. In 1976 McAdam *et al.* compared the opinions of three independent observers about the outcome of varicose vein surgery[14]. Agreement was high, 98 per cent, in the assessment of symptomatic response, but only 60 per cent in assessment of objective visual improvement. Moreover, intraobserver agreement comparing symptomatic response and visual impression was only 30 per cent. This suggests that clinical criteria are an inadequate method of reaching an accurate conclusion about the need for stripping the long saphenous vein.

The present trial was designed to evaluate the results of high ligation without stripping of the long saphenous vein using the objective non-invasive methods which are now available for study of the venous system.

Patients and methods

Patients attending the varicose veins outpatient clinic at the Middlesex Hospital, London, were assessed for saphenofemoral incompetence. This diagnosis was confirmed by duplex Doppler ultrasound in 54 limbs, which were then evaluated before and after surgery.

Duplex scanning was performed using an Acuson 128 (Acuson, Mountain View, California, USA) with a 7·5 MHz linear array transducer and colour flow mapping. Both deep and superficial veins were fully assessed to identify sites of venous incompetence. The examination was performed with the patient standing with weight taken on the contralateral limb; flow within the veins was produced by manual compression of the calf.

Photoplethysmography was used to obtain a functional assessment of the venous system. With the patient sitting, legs hanging dependent, transducers (Medasonics, Fremont, California, USA) were attached to the medial side of the leg 5 cm proximal to the medial malleolus. The patient was asked to perform ten dorsiflexions of the foot to activate the calf muscle pump and to produce venous emptying. On relaxation the venous refilling time was recorded by computer. The procedure was repeated after application of 2·5-cm wide pneumatic tourniquets around the thigh. These were inflated to a pressure of 120 mmHg. Venous refilling times were again recorded at the end of the standard

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exercise. In accordance with the literature a normal venous refilling time was considered to be 20 s or longer[15,16].

All patients were admitted to the Middlesex Hospital under the care of one surgical team. In all cases, under general anaesthesia, a flush saphenofemoral ligation and clearance of all tributaries in the area was performed, accompanied by multiple avulsions of distal varicosities through stab incisions 2–5 mm wide. Operations were performed by a consultant surgeon or senior registrar. After operation Venosan elastic compression stockings (Venosan, St. Gallen, Switzerland) were applied and it was recommended that these should be worn until sutures were removed at the outpatient clinic 7–10 days later.

Patients were recalled 6–12 months later to repeat the venous assessment. Duplex scanning was again performed. The saphenofemoral junction was assessed and presence or absence of flow within the long saphenous vein noted. If retrograde flow of venous blood was identified within the vein an attempt was made to locate the source of this flow. Photoplethysmography was repeated using the same procedure as described above but without tourniquets. Patients were also asked whether they thought that the operation had improved their symptoms. On the basis of the answer they were divided into two groups. Those who were pleased with the outcome of the operation and felt that they had derived benefit from it were labelled as having a satisfactory outcome. Those who still complained of aching and swelling or who had recurrence of varicosities were labelled as having an unsatisfactory outcome.

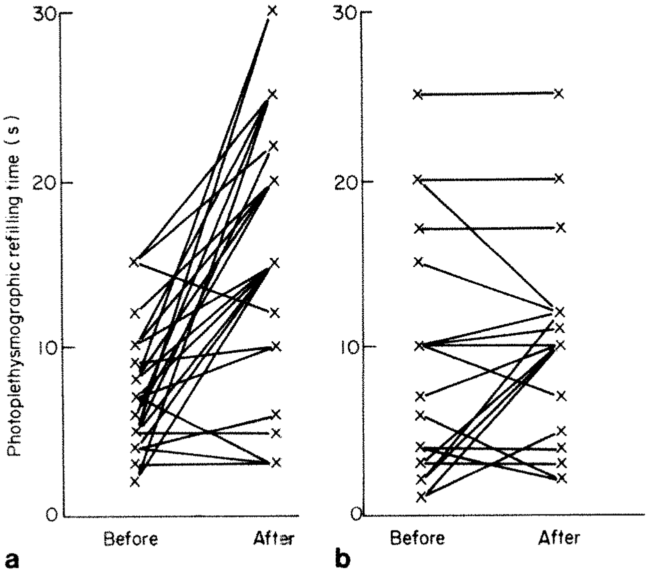

Figure 2 *Venous refilling times measured before and after operation.* **a** *In 31 limbs application of tourniquets before operation normalized refilling times and predicted that the operation would normalize venous function. Refilling times were normal after operation in only 14 cases.* **b** *In 23 limbs application of tourniquets before operation failed to normalize the venous refilling time. None of these achieved normal refilling times after operation*

Results

All 54 limbs studied had saphenofemoral incompetence but no short saphenous incompetence identified by duplex scanning. Four limbs had concomitant deep vein reflux but the remainder had competent deep veins.

Duplex scanning

After operation, duplex scanning revealed that in 52 limbs the saphenofemoral junction had been ligated; however, in two limbs the junction was still patent and retrograde flow of venous blood was still demonstrable (*Figure 1*). A patent saphenofemoral junction was confirmed at a further operation in both cases.

Of the 52 limbs in which the saphenofemoral junction had been ligated, the long saphenous vein could not be identified in 28, presumably having been avulsed or having thrombosed. In the remaining 24 limbs the long saphenous vein was present and reflux of venous blood was demonstrable; in two limbs reflux stemmed from an incompetent mid-thigh perforating vein but in 22 there was reverse flow from just distal to the saphenofemoral junction. This appeared to be fed by small tortuous veins arising from the femoral vein.

Photoplethysmography

Before operation, three limbs had venous refilling times within normal limits (20 s or longer), indicating that the haemodynamic abnormality was minimal, despite the presence of saphenofemoral incompetence and varicose veins. In 20 limbs application of thigh tourniquets failed to normalize venous refilling times (*Figure 2*), indicating that there were incompetent perforating veins present distal to the tourniquet or else incompetence of the deep veins. All of these limbs had persistently abnormal venous refilling times after operation. Before operation application of thigh tourniquets successfully normalized venous refilling times in 31 limbs, suggesting that obliteration of the long saphenous vein would normalize venous function. After operation 14 of these limbs had normal venous refilling times but 17 had persistently abnormal refilling times. In most of these 17 limbs, although refilling times were still less than 20 s, there had been some improvement.

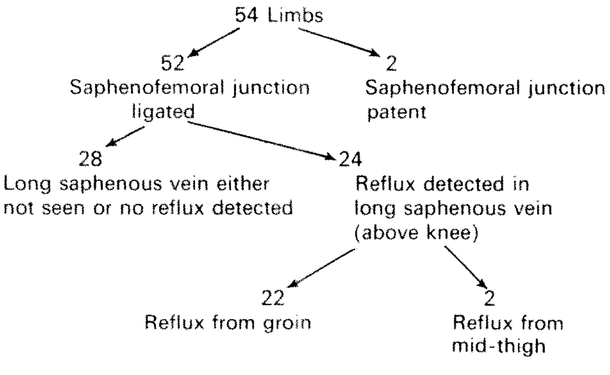
54 Limbs
52
Saphenofemoral junction ligated
2
Saphenofemoral junction patent
28
Long saphenous vein either not seen or no reflux detected
24
Reflux detected in long saphenous vein (above knee)
22
Reflux from groin
2
Reflux from mid-thigh

Figure 1 *Duplex Doppler findings in 54 limbs, 12 months after high ligation plus multiple avulsions of varicosities*

Overall, in those limbs with absence of reflux down the long saphenous vein after operation, there was a statistically significant correlation between the improvement in venous refilling time produced by application of tourniquets before surgery (predicted improvement) and the actual improvement in venous refilling time measured after surgery (observed improvement), with a Pearson's correlation coefficient of $r = 0{\cdot}6$ ($P < 0{\cdot}001$) (*Figure 3*). In those limbs with persistence of reflux down the long saphenous vein after operation, there was no correlation between predicted improvement and observed improvement in venous refilling time.

Subjective outcome

For the group of 31 limbs in which normalization of venous refilling times had been achieved by tourniquets before operation, patients reported that the operation had been satisfactory in 15 limbs but unsatisfactory in 16 limbs. The unsatisfactory result was due to continued swelling in four limbs, persistence of aching in seven and residual or recurrent small varicosities below the knee in five.

A satisfactory outcome was associated with absence of residual reflux in the long saphenous vein after operation whereas an unsatisfactory outcome was associated with persistence of venous reflux ($\chi^2 = 7{\cdot}4$, $P < 0{\cdot}007$). Overall, patients reported a satisfactory outcome in 29 limbs. In this group the operation resulted in a median improvement of 10 s in venous refilling time. In 25 limbs an unsatisfactory outcome was reported and in this group the operation produced a median improvement of only 1 s (*Figure 4*). This difference was statistically significant ($P < 0{\cdot}001$, Mann–Whitney U test).

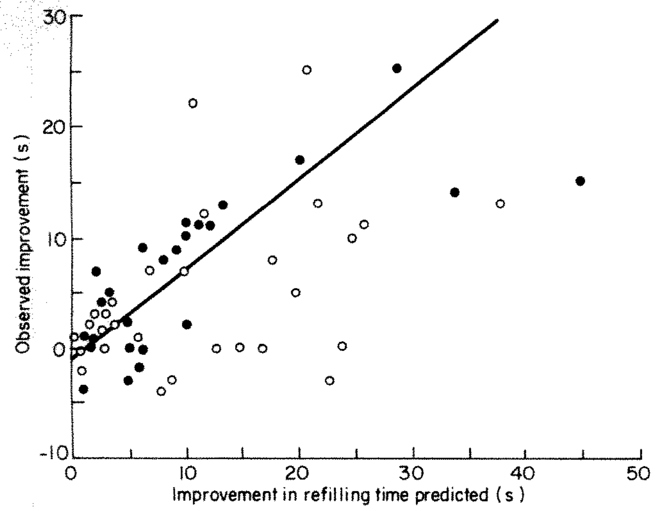

Figure 3 *Correlation between the change in refilling time predicted before operation and the change in refilling time actually observed after high ligation and multiple avulsions in 54 limbs. The limbs with no reflux detected after operation are considered separately from those with persistent reflux. There was a statistically significant correlation (Pearson's correlation coefficient* r = 0·60, P < 0·001*) between predicted and observed refilling times only in the group with no reflux detected after operation.* ●, *No reflux;* ○, *reflux*

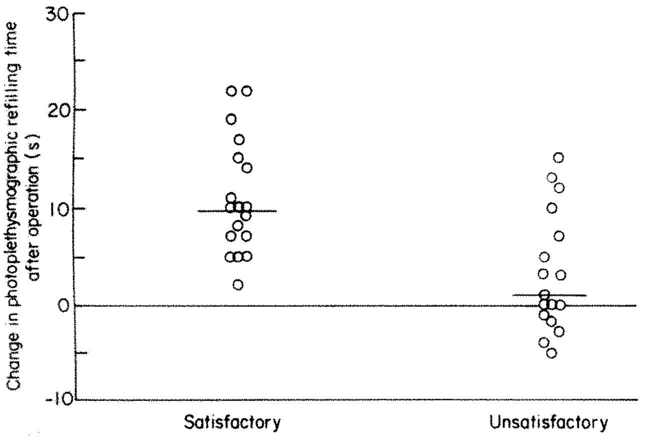

Figure 4 *Change in venous refilling time produced by the operation in the two clinical groups: those with a satisfactory outcome and those with an unsatisfactory outcome. There was a statistically significant difference between the two groups (Mann–Whitney* U *test,* P < 0·01*)*

Discussion

The most surprising finding in this study was the detection after operation of two of 54 patients in whom there had been a failure to ligate the saphenofemoral junction. The Trendelenburg procedure is a highly underrated operation which is often left to junior surgeons to perform. Venous anatomy, even at the saphenofemoral junction, is highly variable[17], and without adequate exposure may be easily misconstrued. In 1961 Haeger reported on the findings of 54 cases requiring reoperation for recurrence of varicose veins[18]. He found that in only six cases had an adequate flush saphenofemoral ligation been previously performed. In three cases a persisting patent saphenofemoral junction was present, despite the fact that the long saphenous vein had reportedly been stripped. He attributed this to duplication of the long saphenous vein. He made measurements of the length of the previous scar and noted that the shorter the scar the higher the incidence of 'operative fault'. He concluded that an incision of less than 6 cm in the groin was inadequate and that a 10 cm incision was optimal to ensure correct identification of venous anatomy. Dodd[19] also recommended an incision of between 10 and 12 cm. In addition, Haeger found that incisions placed distal to the groin crease were associated with inadequate primary operations and recommended an incision as close to the inguinal ligament as possible. All incisions in the present series were made in the groin crease over the inguinal ligament and were on average 3–4 cm in length.

Despite adequate ligation of the saphenofemoral junction, in 24 cases duplex Doppler ultrasound found persistent retrograde flow down the long saphenous vein after operation. In only two limbs was this attributable to an incompetent mid-thigh perforating vein. In the remaining 22 limbs, no residual large tributaries were identified at the level of the groin but tortuous small diameter veins arising from the femoral vein were noted. Recently, Glass has proposed that varicose recurrences are due to 'neo-vascularization' of the ligated long saphenous vein[20]. He reported that construction of a barrier of synthetic mesh and cribriform fascia at the site of transection of the long saphenous vein produced a lower recurrence rate[21]. This was assessed clinically and may be unreliable. The present study supports the concept of neo-vascularization. Narrow pneumatic tourniquets have been shown to occlude the superficial but not the deep veins[22]. Normalization of a fast refilling time by the application of tourniquets therefore indicates that venous reflux is present in the superficial venous system and suggests that surgery to prevent reflux in the superficial veins should normalize venous function. In 31 of the 54 limbs studied, application of tourniquet before operation predicted that prevention of reflux in the long saphenous vein would normalize venous function; the operation performed actually produced this effect in only 14 limbs. The remaining 17 limbs had persistently fast venous refilling times after surgery, suggesting that reflux of venous blood had not been controlled. There was a statistically significant, but not invariable, correlation between reflux detected in the long saphenous vein after operation by duplex scanning and a lack of functional improvement. There were limbs in which reflux was detected after operation but refilling times had been normalized. It is not possible to quantify the amount of reflux seen on duplex scanning, and the reflux detected in these limbs was perhaps too minimal to affect the venous refilling time significantly.

Patient opinion as to the outcome of an operation is dependent on many factors including personality, expectation, indication for operation (for discomfort or cosmetic reasons), circumstances of their hospital stay, and interaction with medical staff. Nevertheless, in the group who reported that the operation had been satisfactory there was a greater improvement in venous function (as measured by the venous refilling time) than in the group dissatisfied with the operation. This difference was statistically significant. A satisfactory outcome was also associated with absence of reflux down the long saphenous vein after operation.

In conclusion, this study suggests that in a large proportion of cases high ligation in combination with multiple avulsion of varicosities fails to prevent reflux of blood and fails to normalize venous function. The long saphenous vein was found still to be patent and incompetent in about half of the limbs operated on and this was associated with persistently abnormal venous refilling times, suggesting that the degree of venous reflux was significant. It remains to be established whether stripping of the long saphenous vein confers better results.

References

1. Mathieson FR. Late results following 293 operations for varicose veins. *Acta Chir Scand* 1953; **105**: 376–89.
2. Lofgren EP, Lofgren KA. Recurrence of varicose veins after the stripping operation. *Arch Surg* 1971; **102**: 111–14.
3. Nabatoff RA. Reasons for major recurrence following operations for varicose veins. *Surg Gynecol Obstet* 1969; **128**: 275–8.
4. Brown DB, Irvine RW, Forrest H. Long-term results of 'high ligation' for varicose veins. *Scot Med J* 1961; **6**: 322–6.
5. Rivlin S. Recurrent varicose veins. *Med J Aust* 1966; **1**: 1097–102.

6. McElwee RS, Maisel B. A study of the results of the surgical treatment of varicose veins. *Ann Surg* 1947; **126**: 350–7.
7. Lofgren KA, Ribisi AP, Myers TT. An evaluation of stripping *versus* ligation for varicose veins. *Arch Surg* 1958; **76**: 310–16.
8. Hobbs JT. Surgery and sclerotherapy in the treatment of varicose veins. *Arch Surg* 1974; **109**: 793–6.
9. Jakobsen BH. The value of different forms of treatment for varicose veins. *Br J Surg* 1979; **66**: 182–4.
10. Woodyer AB, Reddy PJ, Terry T, Dormandy JA. Should we strip the long saphenous vein? In: Negus D, Jantet G, eds. *Phlebology '85*. London: John Libby and Co., 1986: 151–4.
11. Cox SJ, Wellwood JM, Martin A. Saphenous nerve injury caused by stripping of the long saphenous vein. *Br Med J* 1974; **1**: 415–17.
12. Munn SR, Morton JB, MacBeth AAG, McLeish AR. To strip or not to strip the long saphenous vein? A varicose veins trial. *Br J Surg* 1981; **68**: 426–8.
13. Negus D. Should the incompetent saphenous vein be stripped to the ankle? *Phlebology* 1986; **1**: 33–6.
14. McAdam WAF, Horrocks JC, de Dombal FT. Assessment of the results of surgery for varicose veins. *Br J Surg* 1976; **63**: 137–40.
15. Abramowitz HB, Queral LA, FLinn WR *et al.* The use of photoplethysmography in the assessment of venous insufficiency: a comparison to venous pressure measurements. *Surgery* 1979; **86**: 438–40.
16. Kohler TR, Strandness DE. Noninvasive testing for the evaluation of chronic venous disease. *World J Surg* 1986; **10**: 903–10.
17. Corcos L, Peruzzi GP, Romeo V, Fiori C. Considerations of the anatomical variations in the venous system of the lower limbs in varicose disease. *Phlebology* 1989; **4**: 259–70.
18. Haeger K. Technique of high ligation of the long saphenous vein. An analysis of 54 reoperation cases. *Acta Chir Scand* 1961; **122**: 85–92.
19. Dodd H. Recurrent and persistent varicose veins. *Postgrad Med J* 1958; **34**: 73–6.
20. Glass GM. Neovascularisation in recurrence of the varicose great saphenous vein following transection. *Phlebology* 1987; **2**: 81–92.
21. Glass GM. Prevention of recurrent saphenofemoral incompetence after surgery for varicose veins. *Br J Surg* 1989; **76**: 1210.
22. Nicolaides AN, Kakker VV, Field ES, Renney JTG. The origin of deep vein thrombosis: a venographic study. *Br J Radiol* 1971; **44**: 653–63.

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Prospective randomized trial to assess the value of iodine therapy in patients exhibiting high TSH values after thyroidectomy

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During the first year after partial thyroidectomy threre is an appreciable incidence of hypothyroidism judged by FT_4I (free thyroxine index) estimates. The majority of hypothyroid patients become euthyroid untreated but many exhibit clinical features of hypothyroidism during this time. Thyroid remnant recovery is suppressed by administration of T_4 (thyroxine) and its early use invariably commits a patient to T_4 therapy for life. A critical factor in the formation of normal quantities of thyroid hormone is the availability of iodine. Pharmacological doses of iodine (150–200 mg/day) usually suppress thyroid function, whereas physiological doses of iodine (0·2–0·8 mg/day) have been reported to increase T_4.

Patients undergoing partial thyroidectomy for toxic diffuse and non-toxic multinodular goitres were left with a 10 g remnant. At 4 weeks, FT_4I and thyroid-stimulating hormone (TSH) were measured. A raised TSH ($>6\,\mathrm{mU\,l^{-1}}$) determined entry to the trial. Patients included in the trial were asked to eat a normal balanced diet and to avoid food with a high iodine content. Patients giving their informed consent were randomized to receive either chloroform water 5 ml/day (controls) or chloroform water 5 ml/day with 1 mg iodine to be taken for 20 weeks. From the time of supplementation, FT_4I and TSH were measured at 4-week intervals. The mean TSH($\pm$s.d.) and FT_4I($\pm$s.d.) for the placebo and iodine groups are shown. Statistical analysis is by the Mann–Whitney *U* test.

	Time (weeks)					
	4	8	12	16	20	24
TSH						
Placebo ($n=29$)	31(19)	30(20)	25(20)	25(16)	26(18)	10(4)
Iodine ($n=27$)	28(25)	39(34)	30(17)	36(21)	31(14)	32(19)
	P n.s.	P n.s.	P n.s.	P n.s.	P n.s.	P n.s.
FT_4I						
Placebo ($n=29$)	55(22)	59(23)	71(24)	73(20)	74(24)	95(19)
Iodine ($n=27$)	50(16)	44(20)	48(32)	52(23)	53(25)	64(28)
	P n.s.	$P<0{\cdot}01$	$P<0{\cdot}05$	$P<0{\cdot}05$	$P<0{\cdot}05$	$P<0{\cdot}05$

After partial thyroidectomy, the recovery of remnant function as judged by the FT_4I is delayed by iodine therapy given in a physiological dosage.

Long-term follow-up after surgical treatment for hyperthyroidism

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The selection between radio-iodine and surgery in the treatment of hyperthyroidism is a matter of continuous controversy. Radio-iodine in most series leads to a high incidence of hypothyroidism that may occur a long time after treatment. Surgery gives rapid permanent cure with a much lower incidence of hypothyroidism, usually occurring during the first postoperative years. The aim of this investigation was to study, in a prospective long-term (10 years) follow-up, the incidence of hypothyroidism occurring after the first postoperative years.

A total of 179 patients with hyperthyroidism were operated on according to a highly standardized technique and followed at the same department for 5 years with yearly clinical examinations and determinations of thyroid stimulating hormone (TSH) and free thyroxine. Another 5 years later, the patients were called to a new examination using the same parameters.

During the first 5 years, three patients (1·7 per cent) developed recurrent hyperthyroidism and another 68 (38 per cent) developed clinical and laboratory signs of hypothyroidism leading to thyroxine supplementation. One year after surgery this figure was 26·4 per cent, at 2 years 30·3 per cent, at 3 years 35·8 per cent and at 4 years 36·3 per cent. At the additional 5 year follow-up, one patient was found to have recurrence (already diagnosed and treated). Another two patients had been given thyroxine supplementation because of a rise in TSH combined with clinical signs of hypofunction. All the others had normal thyroid hormone levels and were clinically euthyroid.

Life-long follow-up does not appear to be necessary or justified after surgery. There is a notable advantage compared to radio-iodine treatment where life-long follow-up is generally recommended because of a continuously accumulated risk of developing hypofunction.

Rapid intraoperative measurements of intact (1–84) parathyroid hormone in the surgical management of hyperparathyroidism – sequential measurements in patients with multiglandular disease

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The study was undertaken to assess whether or not reliability of rapid intraoperative assay of intact (1–84) parathyroid hormone (iPTH) would allow termination of surgery after removal of one (or several) enlarged parathyroid gland(s) and establishment of a normal intact parathyroid hormone.

iPTH was assayed intraoperatively before removal of enlarged parathyroid gland(s) and 5, 10 and 20 min afterwards (N-tact, pTH, IRMA, Inestar Corp., Minnesota, USA). Results were given within 40 min. The same samples were assayed later using standard methods. Parathyroid glands underwent pathological examination and oil-red-0 staining. Sixty-two patients entered the study: 15 controls (thyroid operations), 40 with primary HPT (32 with uniglandular disease, eight with multiglandular disease) and seven with secondary HPT. All except one forearm graft removal underwent bilateral neck exploration and all were cured.

The rapid assay proved to be less sensitive than the standard method for borderline increased iPTH levels (coefficient of variation = 31·8 per cent). Intraoperatively, among 32 patients with uniglandular disease, five had normal basal intraoperative levels of iPTH, 25 demonstrated a clearcut drop from the supranormal levels to the normal range, but two remained elevated. Among the eight patients with proven multiglandular disease, two reached undetectable levels and two reached upper normal range levels after removal of the first enlarged gland, whereas the other enlarged gland(s) was(were) untouched (90, 307, 322 and 224 + 840 mg respectively). The seven patients with secondary HPT demonstrated a decline in PTH levels suggesting hormone clearance similar to those of primary HPT patients.

Rapid intraoperative assay with intact (1–84) iPTH is not hampered by renal insufficiency but is of questionable utility if the basal intraoperative level of iPTH is normal. The assay may overlook a second (or third) enlarged (adenomatous oil-red-0 staining negative, or hyperplastic) gland, after removal of a first adenoma and establishment of iPTH levels in the normal range. It should not be used as a substitute for bilateral neck surgery.

Risk of neoplasia and malignancy in dominant thyroid swellings

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The incidence of carcinoma in isolated (solitary) thyroid swellings is as high as 20–30 per cent. The risk of malignancy in a dominant thyroid swelling, i.e. a dominant area of enlargement within a multinodular gland, is less well defined. During 6 years, 574 patients with discrete thyroid swellings referred to a surgical thyroid clinical were studied prospectively.

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On the basis of careful clinical examination 395 (69 per cent) swellings were classified as isolated (ITS) and 179 (31 per cent) as dominant (DTS). Of DTS swellings, 65 per cent were solid and 35 per cent cystic. After clinical and cytological assessment 77 (43 per cent) DTS swellings were excised. Of the excised swellings, 45 (58 per cent) were non-neoplastic and 32 (42 per cent) were neoplastic, including 11 malignant lesions. The minimum incidence of neoplasia and malignancy in the total number of 179 DTS swellings was therefore 18 and 6 per cent respectively (assuming all such lesions were removed). It is likely that the true incidence of neoplasia is higher. Dominant thyroid swellings should therefore be regarded with greater suspicion than has been traditional.

Role of thyroid isotope and ultrasound scanning

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Thyroid isotope and ultrasound scans have traditionally been used in the investigation of the solitary thyroid nodule. A prospective study was performed on 68 patients undergoing a total thyroid lobectomy for a solitary thyroid nodule. All patients were initially investigated with thyroid ultrasound and (excepting two pregnant patients) technetium isotope scans.

There were ten malignant nodules: seven papillary, two follicular and one secondary carcinoma. There were 58 benign nodules: 11 neoplastic and 47 non-neoplastic. Isotope scans had been performed in eight of the ten patients with malignant nodules, all of which reported a solitary cold nodule. Ultrasound scans were performed in all ten patients with malignant nodules and, of these, three were reported solid, four solid-cystic, one cystic, one multiple nodules and one normal. Isotope scanning reported a solitary cold nodule in 40 out of 58 benign nodules. Ultrasound scanning reported a solid nodule in 15 out of 58 benign nodules.

This study shows that thyroid isotope and ultrasound scans do not accurately differentiate between benign and malignant conditions. Hence, their routine use in this field should be abandoned if the surgeon has access to fine needle cytology.

Intact parathyroid hormone and normocalcaemic hyperparathyroidism

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Since 1986, 15 patients aged 28–81 years (13 women and two men) have undergone cervical exploration for symptomatic normocalcaemic hyperparathyroidism (serum calcium 2·35–2·59 mmol l^{-1}; normal range 2·25–2·6 mmol l^{-1}). A sensitive immunochemiluminescent assay (ICMA) for serum (1–84) parathyroid hormone (PTH) used in 13 patients revealed high values in all cases (6·7–49·6 pmol l^{-1}; normal range 0·8–5·4 pmol l^{-1}). Urolithiasis was evident in seven patients, musculoskeletal symptoms in six patients and a variety of CNS and gastrointestinal problems in seven patients. At surgery, parathyroid adenomata were removed in 13 patients (gland weights 150–1440 mg). In two patients, four gland hyperplasia were found. Transient postoperative hypocalcaemia was recorded in nine patients. Recurrent laryngeal nerve injury/permanent hypocalcaemia did not occur. Surgical cure, defined by the restoration of elevated intact PTH values to normal was achieved in all cases. At follow-up, improvement in symptoms was recorded in ten patients.

From this study it is apparent that normocalcaemic hyperparathyroidism is a true entity and that an assay for intact PTH permits a confident preoperative diagnosis to be made. The majority of these patients displayed the symptoms and complications usually attributed to hypercalcaemia. Surgical treatment resulted in biochemical cure and a satisfactory resolution of symptoms in a high proportion of patients.

Effect of somatostatin infusion on secretion of parathyroid hormone in primary hyperparathyroidism

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Somatostatin has been found to have an inhibitory effect on the secretion of several pituitary and non-pituitary hormones, including glucagon, insulin and gastrin. The effect of somatostatin on parathyroid hormone (PTH) secretion in primary hyperparathyroidism has not been fully investigated. The aim of this study was to determine the effect of somatostatin infusion in a group of normal individuals and in patients with primary hyperparathyroidism.

Three patients affected by primary hyperparathyroidism and three normal subjects were studied. Somatostatin in normal saline was infused (25 μg h^{-1}) in 120 min. Thereafter for 60 min only normal saline was infused. Blood samples were drawn at regular intervals at times −30, −15, 0, 15, 30, 45, 60, 90, 120, 150 and 180 min. For each time of sample the following parameters were measured: total calcium, phosphorus, magnesium, creatinine, urea, PTH, calcitonin and insulin.

Infusion of somatostatin does not affect the plasma PTH level in normal subjects. A significant increase of PTH in all three patients affected by primary hyperparathyroidism was demonstrated. PTH increased 15 min after somatostatin infusion started, reaching the maximum level at 45 min. The inhibitory action of somatostatin on insulin secretion confirmed the biological activity of the drug used in this study. These preliminary data show a stimulatory action of somatostatin on PTH secretion in patients affected by primary hyperparathyroidism. No effect is seen in normal subjects.

Conventional and three-dimensional thallium–technetium scans in patients with hyperparathyroidism due to multiglandular hyperplasia

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The value of preoperative radionuclide localization in patients with hyperparathyroidism due to a solitary adenoma is acknowledged. In our series, the role of the technique in those patients with hypercalcaemia due to multiglandular hyperplasia remains controversial.

Twenty-five consecutive patients with hyperparathyroidism due to multiglandular hyperplasia were studied from 1984 to date (six primary, 19 secondary). A thallium–technetium scan was performed before surgery. The thallium was administered first and images acquired in two energy windows. A third image was obtained of the thallium contribution in the technetium window, which was subtracted from the technetium views for greater accuracy. The results were correlated with the findings at the time of operation.

In the 21 patients undergoing initial neck exploration, 30 of 70 (42·8 per cent) glands were localized by the preoperative scan. In all three patients with persistent hyperparathyroidism, the single remaining hyperplastic glands were identified by the scan. In our series, the sensitivity of isotope scans for hyperplastic glands was 54 per cent and specificity 73 per cent compared to 100 and 89 per cent, respectively, for adenomatous glands. Weight discrimination may have been a factor: the hyperplastic glands had smaller mean weights (0·92 g) than the adenomatous glands (1·49 g). In addition, emission tomography successfully localized abnormal parathyroid hyperplastic tissue in a third plane in 11 patients. However, an additional gland not visible on the conventional scan was detectable in only one patient.

Thallium–technetium subtraction isotope scanning is non-invasive and inexpensive but only has a limited role in the investigation of enlarged parathyroid glands due to multiglandular hyperplasia, in contrast to previous studies localizing parathyroid adenomas.

Diagnosis of neck metastases from differentiated thyroid cancer by the detection of immunoassayable thyroglobulin in fine-needle aspirates

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Non-thyroidal nodular lesions in the neck, particularly lymph nodes, are a frequent finding which deserve differential diagnosis from metastases of thyroid carcinoma. This may be difficult by fine needle aspirate (FNA) cytology and histology. In this study we assessed the possibility of using thyroglobulin (Tg) measurement in the wash out of the needle employed for the aspiration cytology(FNA-Tg) in 35 non-thyroidal neck nodes of unknown origin.

A first group of patients included 23 subjects with a previous diagnosis and treatment of differentiated thyroid cancer who on whole-body scan had negative cervical lymph nodes ($n = 20$) or other neck masses ($n = 3$). A second group comprised 12 patients with no previous history of thyroid or other neck disease, who presented with one or more cervical nodes. In the first group (patients with differentiated thyroid cancer), FNA-Tg was positive in nine cases and negative in 14 cases. By cytology or histology, ten patients had metastases from thyroid carcinoma, nine of whom had positive FNA-Tg. In the other 13 cases, all with negative FNA-Tg, the final diagnosis was of non-thyroidal metastases in two, of purulent cyst in one, and of chronic reactive lymphadenopathy in ten. In the second group, FNA-Tg was positive in four patients who were found to have metastases from papillary thyroid cancer by histology and negative in eight who had Hodgkin's disease (two cases), oesophageal cancer (one case), renal carcinoma (one case), undifferentiated carcinoma (two cases) and benign lymphadenopathy (two cases).

The results of FNA-Tg were diagnostic of non-thyroidal disease in 22/22 cases and of thyroid metastases in 12/13 cases. In conclusion, this study shows that the finding of elevated immunoassayable Tg concentrations in the FNA is strongly indicative of Tg secreting cells and, therefore, of metastases from differentiated thyroid cancer. FNA-Tg is sometimes more sensitive and specific than FNA cytology.

Prevention of bone fractures by annual intramuscular injection of ergocalciferol in the aged

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A prospective study was started in 1985 to examine the possibilities of preventing bone fractures in aged people by vitamin D treatment. The subjects were given an injection of ergocalciferol (calciferol injection BP, BNF, Evans) (150000 IU) each autumn. This annual injection normalized low serum 25(OH)D concentrations for 1 year. The treatment had a slight effect on serum 24,25(OH)2D levels but no effect on 1,25(OH)2D levels. The controls did not receive any vitamin D supplement.

In both groups there were two different subgroups: those living at home and those living at an institution. After 5 years the numbers of fractures (percentage from subjects) were as follows:

Fracture location	Vitamin D ($n=341$)	Control ($n=458$)
Upper limb	15 (4·4)	46 (10·1)
Lower limb	31 (9·1)	49 (10·7)
Other parts	10 (2·9)	7 (1·5)
Total	56 (16·4)	102 (22·3)

The subjects with vitamin D treatment had fewer fractures, especially in upper limbs, than the controls ($P=0{\cdot}01$, χ^2 analysis; $P=0{\cdot}002$, Fisher's exact test).

The 'toboggan' technique for surgery of substernal goitre

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Substernal goitres are defined as those extending more than four fingerbreadths below the sternal notch with the neck stretched in the operative position or as reaching the lower aspect of the second thoracic vertebra on plain chest X-rays. In our series from 1970 to 1989, among 8243 thyroid operations, 489 (5·9 per cent) were performed for substernal goitres; 6·9 per cent of them crossed the midline behind the trachea or the oesophagus, 16 per cent were toxic and 1·4 per cent malignant.

A cervical approach allowed surgical removal in all cases but one, even when the goitre extended 17 cm into the mediastinum and weighed 1 kg. One case required a sternal split and, in a second case, a subsequent right thoracotomy was required to deliver a mediastinal thyroid mass clearly distinct from the substernal goitre itself.

The surgical technique relies on division of the branches of the upper thyroid artery as the first step, followed by dissection of the upper parathyroid gland and of the recurrent inferior laryngeal nerve close to the cricothyroid membrane. These manoeuvres open a cleavage plane or 'toboggan' on the anterior aspect of the inferior laryngeal nerve. Further dissection is then performed caudally and from behind onwards. Enucleation of the mediastinal part of the goitre is never used as the first operative step.

This method is safe, with a 2 per cent rate of transient hypoparathyroidism and a 0 per cent rate of permanent hypoparathyroidism. Early postoperative vocal cord dysfunction occurred in 10 per cent of cases and recovered in 6 per cent. The remaining 4 per cent were lost to follow-up.

Occurrence of parathyroid carcinoma

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From 1980 to 1990 we operated on 188 patients for hyperparathyroidism (HPT). There was primary HPT in 173 and secondary HPT in 15. The pathological findings of the removed glands showed a parathyroid cancer in ten patients (5·3 per cent) (four other cases were excluded by a recent review), eight men and two women, aged from 30 to 70 years. There were no significant differences in clinical pattern between patients with benign HPT and those with cancer, but in the latter serum calcium levels were generally higher (median value 3·37 mmol l^{-1}) and in two cases >4 mmol l^{-1}. In seven cases the tumour was in the typical site and three patients presented with a mediastinal carcinoma; the excised mass varied from 1·5 to 4·5 cm in size (median 2·5 cm). Surgical treatment always consisted of a superior and inferior parathyroidectomy and ipsilateral hemithyroidectomy (total thyroidectomy in a patient with associated papillary thyroid cancer). Lymphadenectomy was never performed and in no case was chemotherapy or radiation therapy carried out following surgery. Four patients are still alive from 6 months to 6 years from operation. Of these, one shows signs of a recurrence of the disease, two had a second operation because there was evidence of a mediastinal mass and the fourth is free of disease.

Role of flow cytometry in the histological diagnosis of hyperparathyroidism

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Although the pathological diagnosis of hyperparathyroidism is crucial to correct operative strategy, conventional histological examination may be difficult, being observer-dependent. We have examined the role of DNA ploidy of parathyroid tissue, as measured by flow cytometry to determine whether this could contribute to an accurate diagnosis.

Forty-three paraffin-fixed sections of tissue excised from patients with hyperparathyroidism were studied. Histologically this comprised 21 adenomatous and 22 hyperplastic glands. In addition, 14 normal glands and three parathyroid carcinomas were studied. The sections were prepared by dewaxing, rehydration and incubating in RNAase, followed by exposure to pepsin. Single cell nuclei were then obtained by centrifuging and filtering the suspensions. These were subsequently analysed on a Becton-Dickinson FACScan flow cytometer which provided histograms of nuclear DNA content either in the diploid or aneuploid pattern of distribution. Seventeen of 21 (81 per cent) adenomas and 19 of 22 (86 per cent) hyperplastic glands were diploid. All 14 of the normal glands were diploid. Two of 3 (67 per cent) carcinomas were aneuploid.

Most hyperplastic and adenomatous glands were diploid. We consider flow cytometry an unreliable test for the tissue diagnosis of hyperparathyroidism and did not enhance conventional histology in differentiating adenoma from hyperplasia.

Familial hyperparathyroidism and parathyroid carcinoma

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Familial hyperparathyroidism is a well recognized syndrome, often seen with multiple endocrine neoplasia I, occasionally seen with multiple endocrine neoplasia IIA, and rarely found without any evidence of involvement of any other endocrine glands. In these cases there is usually four-gland nodular hyperplasia and malignancy is uncommon. A very small number of families have been reported in which familial hyperparathyroidism is associated with parathyroid adenoma or carcinoma, and in which there is no evidence of involvement of any other endocrine gland.

We have had the opportunity of studying two families first reported 14 years ago, and now report involvement of a further generation, and a screening study of two families using a recently described immunochemiluminescent assay for intact (1–84) parathyroid hormone. In one family there is evidence for involvement of three generations by hyperparathyroidism, but no evidence for involvement of any other endocrine gland clinically or by prolactin assay in either family. The pattern of inheritance is that of an autosomal dominant defect. The hyperparathyroidism in all involved cases presented at a relatively early age, the youngest being 14 years and the oldest being 37 years. Of the eight cases, six were operated on for hyperparathyroidism. Of these, two were malignant, one dying with widespread metastases, and a third case was a probable carcinoma. One of the cases diagnosed in retrospect as probable hyperparathyroidism died at the age of 14 with 'crumbling bones' possibly resulting from parathyroid malignancy. Two affected members of one family were also known to have unusual jaw tumours, one of which was an ossifying fibroma.

We conclude that these families have an inherited liability to parathyroid adenoma and carcinoma which differs clinically from that found in multiple endocrine neoplasia I or II and is likely to be due to a separate genetic defect.

Assessment of parathyroid blood supply with laser Doppler flowmetry during thyroid surgery

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The blood supply of 40 normal human parathyroid glands was studied with laser Doppler flowmetry in 30 patients undergoing operations on the thyroid and parathyroid glands. During continuous flowmeter recording, the inferior thyroid artery and other vessels that might supply the parathyroid glands were occluded so that the routes of parathyroid perfusion could be studied. The effect of surgical dissection was registered. Total occlusion of the main trunk of the inferior thyroid artery resulted in a reduction of the blood flow by one-third. The inferior parathyroid glands were more likely to be affected by occlusion of the inferior thyroid artery than the superior glands. Other major contributors to the blood supply were the superior thyroid artery, the vessels in the thymo-thyroid cord and the thyroid capsule. Laterodorsal dissection of six parathyroid glands from the thyroid lobes reduced the blood flow by roughly half.

These results indicate that the blood supply to the parathyroid is not as dependent on the inferior thyroid artery as has previously been suggested, but that other routes of supply may be equally or, in some cases, even more important. These must be taken into account in the management of parathyroid glands during surgery.

Importance of screening for medullary thyroid cancer

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The morbidity and mortality of medullary thyroid carcinoma depends mainly on occurrence of lymph node metastases. Patients can be cured only in the occult tumour stage. In order to detect family members in families with multiple endocrine neoplasia (MEN II) who are not clinically apparent but may be gene carriers for medullary thyroid carcinoma (MTC), family screening is of importance.

From April 1986 to May 1990, we operated on 34 patients for MTC. Nine patients were suffering from MEN II. In six patients (67 per cent), the tumour was diagnosed due to family screening. Most of the family members are screened once a year by controlling basal and pentagastrin-stimulated calcitonin levels. In all six patients, either stimulated or basal calcitonin levels were elevated.

Clinical examination, ultrasound and scintigraphy were normal. All patients underwent total thyroidectomy and central lymph node dissection. In one patient C-cell hyperplasia was detected histologically and in five patients a multicentric bilateral MTC was found. None of the patients showed involved lymph nodes. The postoperative course was uneventful in all cases and all patients are tumour-free since the operation.

Basal and pentagastrin-stimulated serum calcitonin analysis in MEN II families provides a very effective method to detect medullary thyroid carcinoma in early, curable stage.

Gastrin levels and infantile pyloric stenosis

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The aetiology of infantile pyloric stenosis remains unclear. Aetiological factors of this curious disease may involve hypergastrinaemia or a more generalized disturbance of gastrointestinal peptide secretion.

In this prospective clinical and laboratory study we measured the concentrations of serum gastrin and other factors in 25 infants suffering from the disease. Twenty-five normal babies of the same mean age were used as controls. In the pyloric stenosis group, gastrin measurements were performed in the fasted preoperative and postoperative state as well as in the postprandial postoperative state. In the control group measurements were performed in the fasted and postprandial state.

In the pyloric stenosis group gastrin levels were found to be significantly higher ($P < 10^{-6}$) in comparison with those in the control group in all corresponding states. These gastrin levels were well above those physiologically expected in the early neonatal period. These findings suggest that gastrin may play an important role in the pathogenesis of this unexplained disease.

Re-evaluation of the Captopril test for distinguishing primary hyperaldosteronism from essential hypertension and secondary hyperaldosteronism

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A single-dose Captopril test has been proposed for the diagnosis of primary hyperaldosteronism (PH). We have re-evaluated this test in ten patients with PH (six with hyperplasia, four with adenoma), two with secondary hyperaldosteronism (SH) and nine normokalaemic patients with essential hypertension (EH).

While supine, each patient received 25 mg Captopril orally with blood taken for measurements of plasma aldosterone and plasma renin activity (PRA) before and at 1 and 2 h after ingestion. Plasma aldosterone decreased at 2 h in all patients with EH, being $<416\ \text{pmol}\ \text{l}^{-1}$ ($15\ \text{ng}\ \text{dl}^{-1}$) at 1 and 2 h. In those with PH, plasma aldosterone decreased in only four patients, being $<416\ \text{pmol}\ \text{l}^{-1}$ in three. Plasma aldosterone decreased at 2 h in both patients with SH. PRA was detectable on basal samples in all patients with EH and increased in seven following Captopril. In patients with PH, basal PRA was undetectable in eight and showed no increase at 1 h in seven and at 2 h in eight. In both patients with SH, basal PRA was elevated and rose further following Captopril. Aldosterone:PRA ratio measured at 2 h was >1400 ($50\ \text{ng}\ \text{dl}^{-1}$) in all patients with PH, in none with SH and in only two with EH.

A nomogram of this ratio compared with 2 h plasma aldosterone concentration separated all patients with PH. This test can be used to distinguish primary hyperaldosteronism from essential hypertension and secondary hyperaldosteronism, if interpreted with care.

Gallbladder emptying in patients on long-term octreotide – evidence for rebound hypermotility after stopping treatment

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Treatment with the long acting somatostatin analogue octreotide (Sandoz, Frimley, UK) effectively lowers serum growth hormone concentrations in resistant acromegaly. A side effect of the drug is gallbladder paresis which may lead to gallstone formation. It is not known how quickly the gallbladder recovers after stopping treatment but one possible method of reducing this risk is to omit treatment for 1 day each week to allow complete gallbladder evacuation.

Eight acromegalic patients (four male, four female, mean age 52·5 years, range 35–68) were studied by Tc^{99}-HIDA scintigraphy. Patients were studied both on octreotide (300–600 μg/day) and within 24–96 h of stopping therapy and compared with normal controls.

Mean gallbladder emptying 35 min after a fatty meal in healthy volunteers (six male, four female, mean age 38·6 years, range 27–55) was 45 per cent (s.d. 22) compared to 14 per cent (s.d. 8) in patients on octreotide ($P<0{\cdot}005$, 95 per cent confidence limit 13–49 per cent, unpaired *t*-test). Mean gallbladder emptying 24–96 h after stopping octreotide was 81 per cent (s.d. 12), significantly more than normal controls ($P<0{\cdot}001$, 95 per cent confidence limit 17–54 per cent, unpaired *t*-test), suggesting a rebound phenomenon.

This finding may be of importance because it suggests that gallbladder function returns fully within 24 h. Long-term treatment might be modified to avoid undue risk of gallstones by omitting octreotide for 1 day each week.

New methods for the diagnosis of hypercalcaemia

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Diagnosis of the aetiology of hypercalcaemia can be difficult. Parathyroid hormone-related protein (PTH-rP) is a putative cause of hypercalcaemia or malignancy.

All biochemical profiles performed in a district general hospital over 3·5 months were screened for hypercalcaemia (corrected serum calcium $>2{\cdot}65$ mmol l^{-1}). Possible causes of hypercalcaemia were identified from the patient's history and examination; 25 patients had solid tumours, nine haematological malignancies and 23 features suggestive of hyperparathyroidism. Eleven were receiving thiazide diuretics. Other associations were present in eleven. Twenty-seven had no obvious cause.

Blood samples were obtained for repeat serum calcium and two-site immunoradiometric assays of parathyroid hormone (PTH) and PTH-rP. Fourteen had become normocalcaemic, two with high globulins had a high total but normal ionized calcium. Of the rest, PTH was raised in 38 patients: 20 with known hyperparathyroidism, eight undiagnosed and six receiving thiazides. PTH-rP was raised in 19 patients (17 out of 20 with malignancy).

The two-site immunoassay for PTH-rP shows good discrimination between hyperparathyroidism and solid tumours, and is a major advance in the diagnosis of malignancy-associated hypercalcaemia.

Diagnostic and management difficulties with lactotroph macroadenomas

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Although dopamine agonist therapy has simplified the management of lactotroph macroadenomas, these tumours may rarely pose diagnostic and management difficulty. Two cases are reported.

Case 1 was a 43-year-old man presenting with grand mal epilepsy, a right homonymous hemianopia and bilateral optic atrophy. Computed tomography (CT) demonstrated a large, densely calcified left frontotemporal tumour extending into the pituitary region. At craniotomy this was debulked and histology was very suggestive of a meningioma. Postoperative assessment revealed a serum prolactin level of 450 000 mU l^{-1}, hypercalcaemia (2·9 mmol l^{-1}) with serum parathormone of 2·7 ng ml^{-1} (normal range $=0{\cdot}5$–$1{\cdot}5$ ng ml^{-1}). Immunohistochemistry of the original tumour proved positive for prolactin. A neck exploration confirmed hyperplasia of two parathyroid glands. In view of progressive visual failure, treatment of the large residual tumour with bromocriptine was commenced. This led to CSF rhinorrhoea and pneumocephalus due to extensive erosion of the skull base. This problem persisted despite stopping the bromocriptine and was a major factor contributing to the patient's eventual death after attempts to repair the defect via both trans-sphenoidal and frontal craniotomy routes had failed.

Case 2 was a 14-year-old Nigerian girl presenting with complete blindness and hypopituitarism. CT demonstrated hydrocephalus and a large cystic suprasellar tumour highly suggestive of a craniopharyngioma. However, the serum prolactin level was markedly elevated at 1 350 000 mU l^{-1}. At craniotomy the tumour was debulked and histology confirmed a lactotroph adenoma. A ventriculo-peritoneal shunt was inserted to relieve the hydrocephalus. The extensive residual tumour did not respond significantly to bromocriptine treatment and serum prolactin levels remained at $\approx 200\,000$ mU l^{-1}.

These case reports indicate the highly variable radiological features of lactotroph macroadenomas.

Parathyroid hormone-related protein expression in breast cancers

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Hypercalcaemia develops in 10–15 per cent of breast cancers[1]. Parathyroid hormone-related protein (PTH-rP) has been isolated from solid tumours associated with humoral hypercalcaemia of malignancy but the mechanism of hypercalcaemia in breast cancer is said to be local destruction of bone[2].

Using a rabbit polyclonal antibody to the PTH-rP 34–67 mid-molecule, a range of breast carcinomas have been studied for the presence of PTH-rP in a three-stage streptavidin-biotin complex immunoperoxidase method. Fifty-five out of 106 (52 per cent) unselected breast cancers exhibited extranuclear cytoplasmic staining for PTH-rP. A second selected group of primary breast cancers from 72 women who have developed bone metastases with ($n=25$) or without ($n=47$) hypercalcaemia over a 5-year follow-up period were also studied.

Thirty out of 47 (64 per cent) carcinomas which have developed bone metastases without hypercalcaemia stained compared to 22 (88 per cent) of the 25 cancers associated with bone metastases and hypercalcaemia ($P<0{\cdot}002$ linear test for trend).

Breast tumours expressing PTH-rP are more likely to metastasize to bone and local production of PTH-rP may be responsible for the hypercalcaemia associated with bone metastases in breast cancer.

1. Waxman J. Hypercalcaemia – new mechanism for old observations. *Br J Cancer* 1990; **61**: 647–8.
2. Hickey RL, Samaan WA, Jackson GL. Hypercalcaemia in patients with breast cancer. *Arch Surg* 1981; **116**: 545–52.

Correspondence

Non-steroidal anti-inflammatory drugs and complicated diverticular disease: a case–control study

Sir

We read with interest the paper by Campbell and Steele (*Br J Surg* 1991; **78**: 190–1). As in the previous retrospective case control study of Langman *et al.*[1], the authors describe a strong association between ingestion of NSAIDs (non-steroidal anti-inflammatory drugs) and serious complications of diverticular disease. Langman and collaborators associated NSAID intake with bleeding from diverticular disease in addition to septic complications, while the present report recorded both bleeding and perforation as a complication. It would be helpful to know if the Aberdeen data demonstrated a higher incidence of bleeding in those patients presenting with complications of diverticular disease who were taking NSAIDs compared with those who were not.

In our own recently reported prospective study[2] we defined a strong association between serious septic complications and NSAID intake, but patients on these drugs did not present more frequently with bleeding. This point is relevant as we have suggested that the possible mechanism for the NSAID effect in diverticular disease is related to an inhibition of the inflammatory response resulting in failure to localize the disease process.

Corticosteroids have also been related to the septic complications of diverticular disease[3]. As these drugs are commonly prescribed in combination with NSAIDs, it is also important to establish whether the Aberdeen data corrected for this possible source of bias.

None the less, this study, in conjunction with the previous ones[1–3], underlines the strong association between NSAIDs and complications of diverticular disease. Perhaps given this clear association, the time has come to consider known diverticular disease as a relative contraindication to prescription of these agents.

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1. Langman MJS, Morgan L, Worral A. Use of anti-inflammatory drugs by patients admitted with small or large bowel perforations and haemorrhage. *Br Med J* 1985; **290**: 347–9.
2. Wilson RG, Smith AN, Macintyre IMC. Complications of diverticular disease and non-steroidal anti-inflammatory drugs: a prospective study. *Br J Surg* 1990; **77**: 1103–4.
3. Corder A. Steroids, non-steroidal anti-inflammatory drugs and serious septic complications of diverticular disease. *Br Med J* 1987; **295**: 1238.

Author's reply

Sir

Thank you for giving us the opportunity to reply to the letter from Mr Wilson and his colleagues regarding our paper on 'non-steroidal anti-inflammatory drugs and complicated diverticular disease'.

With regard to their first point, we did not find a higher incidence of bleeding in the patients who were taking non-steroidal anti-inflammatory drugs. Indeed, only two out of the 24 on such medication presented with bleeding compared with three out of the 26 patients with complicated diverticular disease.

As Mr Wilson and his colleagues correctly point out, corticosteroids are also related to complicated diverticular disease, but in fact none of our study patients was on these drugs.

We very much enjoyed reading the paper from Edinburgh, and we would strongly endorse the conclusions drawn in this letter.

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Stercoral perforation of the colon

Sir

We read with interest the review by Messrs Serpell and Nicholls on stercoral perforation of the colon (*Br J Surg* 1990; **77**: 1325–9) having recently managed two such cases, both of whom reperforated after limited colonic resection with exteriorization.

The paramount impression we have gained from these cases is that, while the initial operation coped with the perforation, it failed singularly to address the aetiology of that perforation, and we question whether these patients may have been better served by undertaking total colectomy and ileostomy, preserving the rectal stump for later ileorectal anastomosis. Such a strategy would negate the risk of further early stercoral perforation, as experienced both by ourselves and the authors, and also address the problem of chronic constipation that has already resulted in a life-threatening complication.

To advocate limited resection there seems to be two prerequisites, firstly that there is an effective method by which the proximal colon can be cleared at operation, and secondly that after re-anastomosis recurrence of constipation can be adequately treated. While orthograde lavage is undoubtedly useful as a peroperative bowel preparation in emergency colectomy, evidence of its success largely depends on reported anastomotic leak rate, and it is uncertain whether effective colonic cleaning could be achieved in the presence of scybalous masses throughout the colon. Furthermore, it is unknown whether such patients may have a higher risk of leakage from the caecotomy or appendicostomy necessary to undertake this procedure. With regard to the second point the literature is unhelpful, failing to report the long-term follow-up of patients undergoing emergency resection for stercoral perforation. It is recognized, however, that limited resection in the elective treatment of constipation has generally given poor results[1].

To undertake subtotal colectomy in these patients, the risks must necessarily be less than those associated with limited resection. In this respect the closest comparison to be drawn is with the experience gained in extended colectomy for left colonic obstruction, where subtotal colectomy has been associated with lower mortality than local resection[2,3].

While realizing that the infrequency of stercoral perforation may make the case impossible to prove, we write to raise the issue.

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1. Preston DM, Hawley PR, Lennard-Jones JE, Todd IP. Results of colectomy for severe idiopathic constipation in women (Arbuthnot Lane's disease). *Br J Surg* 1984; **71**: 547–52.
2. Wilson RG, Gollock JM. Obstructing carcinoma of the left colon managed by subtotal colectomy. *J R Coll Surg Edinb* 1989; **34**: 25–6.
3. Morgan WP, Jenkins N, Lewis P, Aubrey DA. Management of obstructing carcinoma of the left colon by extended right hemicolectomy. *Am J Surg* 1985; **149**: 327–9.

Notices and announcements

2–4 October 1991
12th International Symposium on Computer Assisted Decision Support & Database Management in Anesthesia, Intensive Care and Cardiopulmonary Medicine
Rotterdam, The Netherlands
Information: Dr Omar Prakash, Thorax Centre, Erasmus University, 3000 DR Rotterdam, The Netherlands

2–5 October 1991
Course in Surgical Oncology; Royal Marsden and Westminster Hospitals
London, UK
Information: The Manager, Education and Conference Centre, Royal Marsden Hospital, Fulham Road, London SW3 6JJ, UK

7–10 October 1991
5th Congress of the European Society for Organ Transplantation
Maastricht, The Netherlands
Information: Congress Secretariat, Conference Agency Limburg, c/o University Hospital Maastricht, PO Box 1918, 6201 BX Maastricht, The Netherlands

9–12 October 1991
Principles of Colon and Rectal Surgery
Minneapolis, Minnesota, USA
Information: Continuing Medical Education, University of Minnesota Medical School, Radisson Hotel Metrodome, Suite 107, 615 Washington Avenue Southeast, Minneapolis, Minnesota 55414, USA

10–11 October 1991
GI Tract Laparoscopic Surgery Meeting
Liege, Belgium
Information: Catherine Marissiaux, Clinique Saint-Joseph, Chirurgie de l'Appareil Digestif, Rue de Hesbaye 75, B-4000 Liege, Belgium

20–25 October 1991
American College of Surgeons Annual Clinical Congress
Chicago, USA
Information: Sally Gerneski, American College of Surgeons, 55 East Erie Street, Chicago, Illinois 60611-2797, USA

30 Oct–3 Nov and 3 Nov–6 Nov 1991
International Conference of Gastroenterology
Hong Kong then Beijing, China
Information: Conference Secretariat, 12/F Kaiseng Commercial Centre, 4–6 Hankow Road, Kowloon, Hong Kong

30 October–3 November 1991
Course/Workshop in Blood Vessel Imaging Using Ultrasound Techniques
Torquay, UK
Information: Mr K. N. Humphries, Blood Vessel Imaging Course, 10 Swale Drive, Chandlers Ford, Hampshire SO5 3QY, UK

5–8 November 1991
Intensive Practical Course in Phlebology
Houston, Texas, USA
Information: N.A.S.P., 204 N. El Camino Real, E-234, Encinitas, CA 92024, USA

7 November 1991
'Vascular Training Would Be Improved By A Specific Diploma'
London, UK
Information: Mr J. H. N. Wolfe, Secretary, London Vascular Debating Group, St. Mary's Hospital, Praed Street, London, WC2 1NY, UK

7–9 November 1991
3rd Combined Meeting of the Nederlandse Vereniging voor Thoraxchirurgie and the Deutsche Gesellschaft für Thorax-, Herz- und Gefässchirurgie
Maastricht, The Netherlands
Information: Organizing Secretariat, Conference Agency Limburg, University Hospital Maastricht, PO Box 1918, 6201 BX Maastricht, The Netherlands

7–10 November 1991
XVII European Society for Medical Oncology Conference
Lyon, France
Information: Michel Clavel, MD, XVII Congress ESMO, CLB, 28, rue Laennec, 69373 Lyon Cedex 08, France

8 November 1991
Vascular Symposium. Angioplasty, Thrombolysis & Angioscopy — A Minimally Invasive Approach to Arterial Disease
Edinburgh, UK
Information: Sheila Heap, Meadox (UK) Ltd., Matthew House, Matthew Street, Dunstable, Bedfordshire LU6 1SD, UK

12–14 November 1991
1st European Conference on Tissue Banking and Clinical Application
Berlin, Germany
Information: Mr Rudiger von Versen, German Central Tissue Bank, ITT, Medical Faculty (Charite), Humboldt-University Berlin, Schumannstr. 20/21, D-1040 Berlin, Germany

14–16 November 1991
10th Annual WBAMC Trauma Symposium
El Paso, Texas, USA
Information: Mrs Marty May, Trauma Service/SICU, Department of the Army, William Beaumont Army Medical Center, El Paso, Texas 79920-5001, USA

15–16 November 1991
Laparoscopic Cholecystectomy Workshop
Edinburgh, UK
Information: Mrs Maureen Webb, Royal College of Surgeons of Edinburgh, Nicolson Street, Edinburgh EH8 9DW, UK

17–23 November 1991
Surgery of the Pancreas, Liver and Biliary System
Edinburgh, UK
Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

19–22 November 1991
7th International Symposium on Cardiopulmonary Urgencies and Emergencies
Rotterdam, The Netherlands
Information: Dr O. Prakash, University Hospital Rotterdam, dr. molewaterplein 40, 3015 GD Rotterdam, The Netherlands

3–5 December 1991
6th International Workshop on Therapeutic Endoscopy
Hong Kong
Information: Dr J. W. C. Leung, Department of Medicine, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong

12–13 December 1991
1st EEC Conference on Pain Research
Brussels, Belgium
Information: M. Staquet, Rue Heger-Bordet, 1, B-1000 Brussels, Belgium

5–8 January 1992
Postgraduate Gastroenterology Course
Oxford, UK
Information: Dr D. P. Jewell, Radcliffe Infirmary, Oxford OX2 6HE, UK

17–19 January 1992
XXVIII Head and Neck Course
Liverpool, UK
Information: Mrs B. Cowley, Department of Otorhinolaryngology, University of Liverpool, Royal Liverpool Hospital, PO Box 147, Liverpool L69 3BX, UK

1–3 April 1992
Association of Surgeons of Great Britain and Ireland Annual Meeting
Jersey
Information: Ms Caroline Ross, The Royal College of Surgeons, 35/43 Lincoln's Inn Fields, London WC2 3PN, UK

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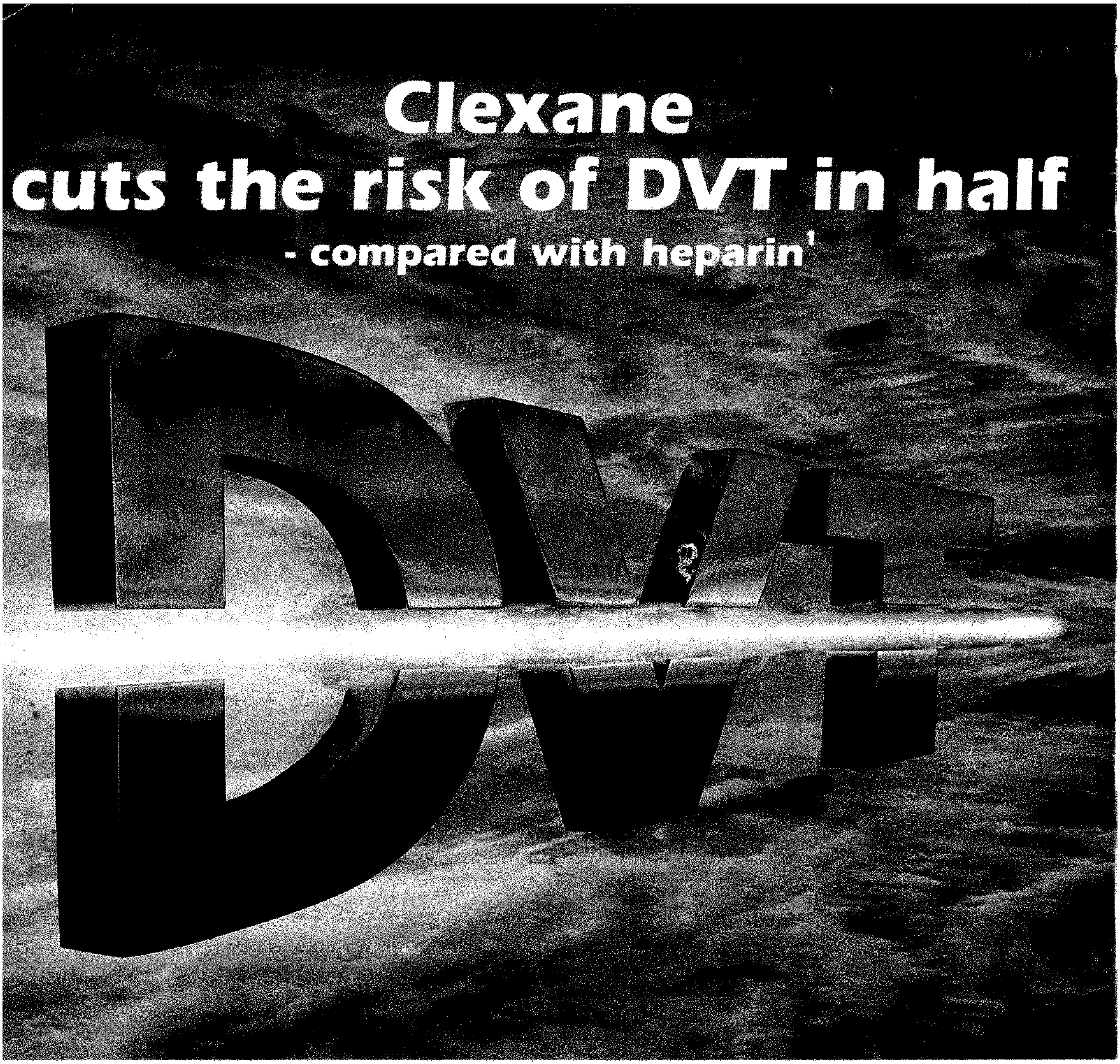

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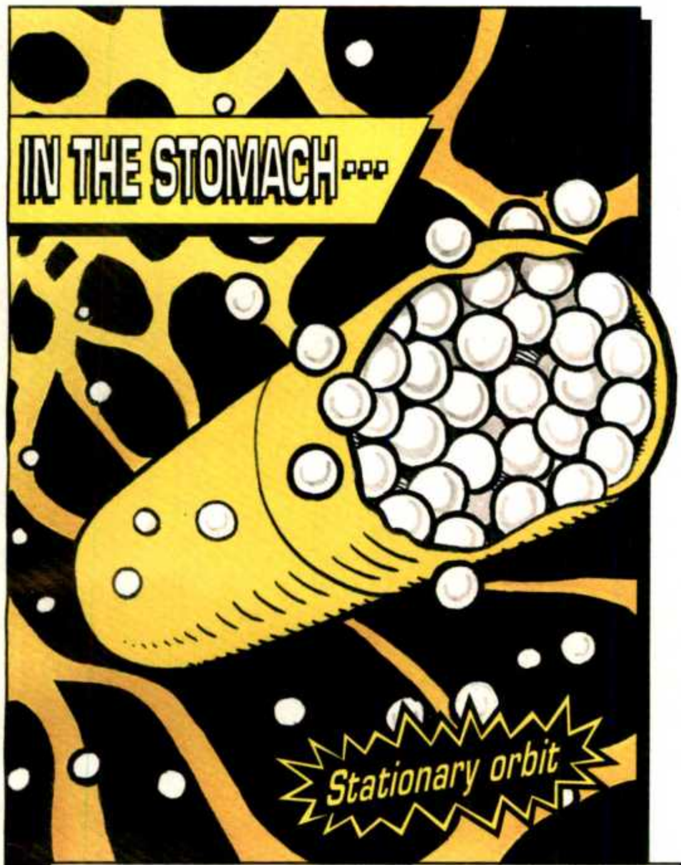

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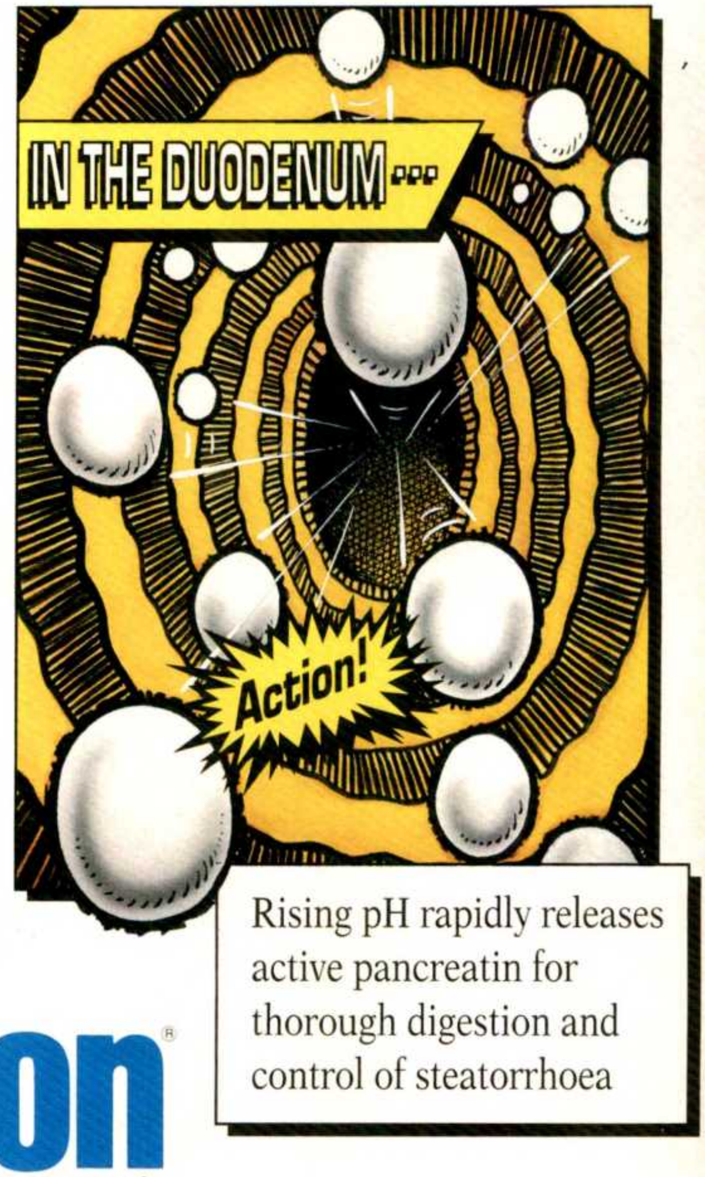
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References

1. Stead RJ et al. *Thorax* 1987;**42**:533-537. 2. Beverley DW et al. *Arch Dis Child* 1987;**62**:564-568.

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13.00-14.30	LUNCH
14.30-15.30	Live Demonstration of Hernia Repair *John Corbett*
15.30-16.00	TEA
16.00-16.30	Review of Laparoscopic Cholecystectomy in the UK *John Saunders, Western General Hospital, Edinburgh*
16.30-17.00	Advances in Thorascopic Surgery *W. Fountain, Harefield Hospital, London*
17.00	BSSG Business Meeting
19.30 for 20.00	SYMPOSIUM DINNER

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Leading article

Br. J. Surg. 1991, Vol. 78, October, 1153–1155

Current status of carotid endarterectomy

The brain receives its blood supply through four arteries, the two internal carotid and the two vertebral arteries. Occlusion of one of these vessels only affects cerebral blood flow if the circle of Willis is deficient. Consequently, the simplistic hope that relieving a partial obstruction of one carotid artery will improve cerebral blood flow and reduce the risk of stroke has never had a sound physiological basis. However, when it became clear in the 1950s[1] that many strokes were caused by emboli derived from atheromatous disease at the bifurcation of the carotid artery, surgeons argued strongly that removal of this disease would reduce the risk of stroke. This was not just a pipe-dream, for surgical removal of disease at the carotid bifurcation is a practical possibility because it is usually limited to the first 2–3 cm of the internal carotid artery, with healthy vessels above and below.

The logic of the argument seemed undeniable, and consequently the number of carotid endarterectomies (CEs) performed throughout the world steadily increased. By the mid 1980s CE was the most common arterial operation performed in the USA[2]. This boom was encouraged by the publication of many individual uncontrolled series of operations which showed that the procedure could be performed with very low rates of mortality and morbidity, and further expanded by the introduction of CE for asymptomatic disease. It was this latter expansion of the indications for CE that made many surgeons, and still more neurologists, review the evidence justifying its use. In spite of the logic, and in spite of the many published personal series, the evidence was found to be inadequate and certainly not good enough to justify 100 000 operations each year. Consequently, in the mid 1980s the clinical trialists moved in. Four large multicentre trials were started, two to study symptomatic disease and two to study asymptomatic disease. The first two have been reported, and to the vascular surgeons' relief and barely concealed delight show that they had been right from the beginning.

Description of trials

MRC European Carotid Surgery Trial (ECST)[3]. This was designed to assess the value of CE in patients who, after having a carotid territory, non-disabling ischaemic stroke, transient ischaemic attack (TIA) or retinal infarct, are found to have a stenotic lesion in the relevant (ipsilateral) carotid artery.

North American Symptomatic Carotid Endarterectomy Trial (NASCET)[4]. This was designed to answer the question: does CE, despite the perioperative risk of stroke or death from any cause, reduce the overall risk of fatal and non-fatal ipsilateral carotid stroke among symptomatic patients with high grade carotid stenosis (70–99 per cent)?

Asymptomatic Carotid Atherosclerosis Study (ACAS)[5]. This was designed to determine whether CE plus aspirin and risk factor modification in patients without symptoms reduce the incidence of carotid-derived TIAs or cerebral infarction when compared against aspirin and risk factor modification alone.

Veterans' Administration Asymptomatic Carotid Stenosis Trial[6]. This was designed to answer the question: does CE plus aspirin in patients without symptoms reduce the incidence of TIAs or stroke when compared with aspirin alone?

Present status of trials

MRC European Trial of Symptomatic Disease[3]. The results of the first analysis were reported in May 1991. They show that CE confers a significant benefit in patients with severe (70–90 per cent) stenosis. Of 2518 randomized patients, 778 were in the severe category and 455 were treated surgically; 7·5 per cent had a stroke or died within 30 days of surgery, but during the next 3 years only another 2·8 per cent had strokes, compared to 16·8 per cent of the control patients, a sixfold reduction

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($P<0.0001$). However, the analysis also showed that CE conferred no benefit on patients with mild (0–29 per cent) stenosis. Thus for mild and severe stenosis the trial has been stopped, but it continues to assess those with moderate stenosis (30–69 per cent) as the balance of surgical risk against eventual benefit in this group remains unclear. The incidence of stroke or death during the first 30 days following randomization to the CE group (7·5 per cent) seems quite high, but the incidence in the control group was 5 per cent.

North American Symptomatic Carotid Endarterectomy Trial (*NASCET*)[4]. The results of this study have not yet been published in a peer review journal but they have been circulated to all members of the American Vascular Societies[4]. The results are remarkably similar to those of the European Trial. There were 595 patients; 300 had CE and 295 were controls. Between the time of randomization and 30 days later, 5 per cent of the CE group and 3 per cent of the control group suffered a stroke or died. Thereafter an interim analysis, performed at an average follow-up time of 18 months, revealed that the incidence of death and stroke in the CE group was 2 per cent, compared to 21 per cent in the control group ($P < 0.001$), a tenfold reduction. The interim analysis of the patients with 30–69 per cent stenosis was inconclusive, so this section of the trial continues.

Asymptomatic Carotid Atherosclerosis Study (*ACAS*)[5]. The results of this study have not yet been reported. It was started in 1988 and 810 patients have so far been randomized. Surgeons participating in the study must carry out more than 12 CEs each year with a mortality and morbidity rate of less than 3 per cent. Each surgeon's complication rate is regularly reviewed. So far the overall surgical mortality and stroke rate is less than 3 per cent. If it rises above this figure the trial will be stopped. When the 117 participating surgeons' results before the study were analysed, their combined mortality and stroke rates after 1511 CEs for asymptomatic stenosis were 0·8 per cent and 0·9 per cent, respectively. The results of this study are unlikely to be presented until 1994–1995.

Veterans' Administration Asymptomatic Carotid Stenosis Trial[6,7]. This study was carried out from 1983 to 1987. The results, based on a full 5-year follow-up, are expected later this year. There have been 444 patients randomized, 211 to CE and 233 to aspirin[7]. The surgical group mortality rate was 1·9 per cent (all cardiac), and the stroke rate was 2·4 per cent. Rumours abound; most suggest that this trial will show that CE is beneficial, but we must wait for the published results.

Comment

Two large multicentre trials, conducted by neurologists and epidemiologists as well as surgeons, have clearly shown that CE for patients who are found to have a 70–99 per cent stenosis of their internal carotid artery after suffering a TIA or minor stroke reduces the subsequent incidence of stroke by six to ten times. Both studies have shown that the risks of death or a second stroke in the first 30 days after beginning the patient's investigations, regardless of the treatment offered, are not insignificant; 5–7 per cent for CE, 3–5 per cent for controls. Surgery clearly adds at least 2–3 per cent to the risk, so the risks of surgery must be kept to a minimum. The restrictions of the American trialists[5] and the advice of the Stroke Council of the American Heart Association[8] should be applied to all surgeons who practice CE. The combined 30-day operative mortality and stroke rate for patients who have had a previous minor stroke should be less than 7 per cent; for patients who have suffered TIAs it should be less than 5 per cent; and (if the asymptomatic trials show CE to be of benefit) for patients with asymptomatic stenosis greater than 60 per cent, less than 3 per cent. The American College of Physicians has similarly stated that the maximum acceptable complication rates for patients with TIAs treated by CE should be a mortality rate of less than 1 per cent and a stroke rate of less than 3 per cent[9].

How can a referring physician know an individual surgeon's results? All vascular surgeons should keep a running up-to-date record of all the CEs they perform so that they can quote their results at any time. As we are talking about 30-day results, and as strokes and death very rarely occur after the fifth postoperative day, keeping such a record is not difficult. Furthermore, as most published studies show that surgeons who perform fewer than 12–15 CEs per year have poor results, every surgeon should also quote the number of procedures they perform each year, and each personal audit should be based on no less than 50 operations, preferably 100. Now that we know that CE for symptomatic stenosis greater than 70 per cent has a significant effect on the incidence of subsequent stroke, we should ensure that all general practitioners, physicians and neurologists are well aware of this fact and that patients presenting with symptoms are properly investigated. Duplex scanning – both the equipment and the technicians – should be available in all major hospitals, for this is the simplest, quickest and most accurate of the screening methods. The vascular surgeons in the UK should be doing many more CEs, but they will only be referred suitable patients if they are prepared to subject themselves to a continuing accurate audit that is easily available to all referring physicians.

One final comment must be made. Two extremely expensive controlled trials have been conducted by our demand, and that of government bodies and medical insurance companies, to prove that CE is worthwhile. The results are identical to the individual studies of both medical and surgical treatment published over the past 15 years which have shown that surgery can have a combined mortality and stroke risk of less than 5 per cent[10], and thereafter a stroke risk of less than 1 per cent per annum[11], compared to a stroke risk when on medical treatment of 5 to 10 per cent per annum[12]. These are studies on which many surgeons and physicians were prepared to base their judgement that CE is worthwhile. None of these publications were controlled trials, and so were unacceptable to the scientific community and unsuitable for the currently popular meta-analysis, but they clearly, when combined and compared, contained the truth. Has the time come for the statisticians to look at ways of comparing uncontrolled studies and individual experiences, when they abound in large numbers, to avoid the massive costs of large clinical trials?

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1. Gunning AJ, Pickering GW, Robb-Smith AHT, Ross-Russell R. Mural thrombosis of the internal carotid artery and subsequent embolism. *Q J Med* 1964; **33**: 155–95.
2. Pokras R, Dyken ML. Dramatic changes in the performance of endarterectomy for diseases of the extracranial arteries of the head. *Stroke* 1988; **19**: 1289–90.
3. European Carotid Surgery Trialists Collaborative Group. MRC European Carotid Surgery Trial, interim results for symptomatic patients with severe (70–90%) or with mild (0–29%) carotid stenosis. *Lancet* 1991; **337**: 1235–43.
4. Clinical Alert. *Benefit of Carotid Endarterectomy for Patients with High Grade Stenosis of the Internal Carotid Artery.* National Institute of Neurological Disorders and Stroke Publication, 1991.
5. Asymptomatic Carotid Atherosclerosis Study Group. Study design for randomised prospective trials of carotid endarterectomy for asymptomatic atherosclerosis. *Stroke* 1989; **20**: 844–9.
6. A VA Cooperative Study. Role of carotid endarterectomy in asymptomatic carotid artery stenosis. *Stroke* 1986; **17**: 534–9.
7. Towne JB, Weiss DG, Hobson RW. First phase reports of co-operative VA asymptomatic carotid stenosis study – operative morbidity and mortality. *J Vasc Surg* 1990; **11**: 252–8.
8. Beebe HG, Clagett GP, De Weese JA *et al.* Assessing risk associated with carotid endarterectomy, a statement for health professionals by an Ad Hoc Committee on Carotid Surgery Standards of the Stroke Council, American Heart Association. *Stroke* 1989; **20**: 314–15.
9. Interim assessment: carotid endarterectomy, report of the American Academy of Neurology, Therapeutics and Technical Assessment Subcommittee. *Neurology* 1990; **40**: 682–3.
10. Browse NL, Ross-Russell R. Carotid endarterectomy and the Javid shunt. The early results of 215 consecutive operations for transient ischaemic attacks. *Br J Surg* 1984; **71**: 53–7.
11. Stewart G, Ross-Russell R, Browse NL. The long term results of carotid endarterectomy for transient ischaemic attacks. *J Vasc Surg* 1986; **4**: 600–5.
12. The ESPS Group. The European Stroke Prevention Study. *Lancet* 1987; **ii**: 1351–4.

Association of Surgeons of Great Britain and Ireland

Br. J. Surg. 1991, Vol. 78, October, 1156–1158

A meeting of the Association of Surgeons of Great Britain and Ireland took place in Oxford on 3–5 April 1991. The President of the Association, Mr Malcolm H. Gough, was in the chair.

Surgical training: a report to the Association of Surgeons of Great Britain and Ireland

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During the author's tenure (1990–1991) of the British Journal of Surgery *Travelling Fellowship of the Association of Surgeons of Great Britain and Ireland, a study was made of surgical training in this country and abroad. This report outlines certain beneficial changes which may be made in UK training programmes.*

When, 100 years ago, Lawson Tait delivered a lecture on the training of a surgeon, he said that the surgical apprentice must be 'taught how to use his hands. I should set him so many hours in the week into the shop of the village carpenter, and I would have him trained to use a saw, a chisel and a plane'[1]. Shrewd clinical judgement and manual dexterity were the essential attributes of the surgeon of Tait's time, and apprenticeship was the natural situation in which to learn these skills. It continues to be the mainstay of surgical training but, with 100 years of development in surgical science and practice, the question is whether present methods can be relied on to train the surgeons of the 1990s.

In spite of the activities of surgical training committees over the past 20 years, we are confronted with the conclusion of an American visitor in 1990 that 'graduate medical education in Britain is a brutal enterprise – service duties seem to preclude all but informal and haphazard education'[2]. In surgery we have to remember that the Confidential Enquiry into Perioperative Deaths (CEPOD) of 1987 found that between 30 and 50 per cent of deaths in three regions had received no consultant input at any stage: 'in some hospitals the trainees practised to all intents as pseudo-consultants'[3]. Two recent reports of registrar experience showed considerable deficiencies in supervision of work in the theatre[4,5].

For too long it has been assumed that, provided trainees are sharing in the provision of a service, then training must be being received, but 'learning by doing, in the absence of a teacher to provide guidance and feedback, has the inherent potential for learning the wrong thing in the wrong way'[6]. At a time when general surgery faces unusual challenges (in the shape of remarkable developments in practice) and difficulties (with changes in management, bed closures and additional demands on consultants), it is necessary to look afresh at the character of a sound training programme, and how it can be achieved.

The first year

The first year of the surgical trainee is of particular educational importance. It is then that good clinical and technical habits should be acquired, yet there is evidence that opportunities for teaching and study are often inadequate[6]. The first 6 months should be spent with a surgeon who has offered to act as mentor to trainees, and is prepared (and given the time and contractual recognition) to teach basic operating skills. The second 6 months should be spent with another trainer. This should enable the two trainers together to make a fair assessment of the judgement and technical ability of the trainee, and to offer useful advice for the future.

Subsequent basic training

Those who show promise will proceed into the second and later years of basic training, entering a planned 6-monthly rotation through general and specialist departments. Supervision will still be vital, with the observant teacher needing to nurture self-reliance in some, while curbing over-confidence in others.

A good training programme requires more structured tuition than has so far been usual.

Study. It should be customary for the trainee, when assisting, to know the anatomy of the part and the principles of the procedure from study of an atlas, so that a useful tutorial can take place. Interest can be stimulated by giving the trainee a part of the operation to perform.

Day surgery. The volume of day surgery seems bound to increase and is practised on just those patients whose hernia repairs and high saphenous ligations are staples of basic training. Because close supervision of a trainee operating in this area is essential, much valuable teaching can be accomplished in this setting.

Simulation workshops. The increasing use of simulation workshops is an important development. There must be concern over the widely variable results of large bowel anastomoses revealed in recent surveys[7,8]; this is largely because some trainees see many anastomoses but are actually assisted to perform only a few. This is precisely the deficiency that a workshop is designed to correct because, away from the preoccupations of the theatre, there is time for the lecturer to demonstrate and discuss anastomotic technique. Every trainee can practise the movements and test the results of suturing, and learn at first hand that safe anastomosis depends on practised skill and attention to detail. When the essential move is made to the theatre, the trainee can concentrate on the aspects

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of technique only demonstrable in the living patient, and will be prepared to perform the anastomosis itself expeditiously and safely. Management will appreciate that preliminary simulation promotes good use of theatre time.

Emergencies. A vital element in basic training is wide experience among patients admitted as an emergency. We cannot afford for this to be seen as a poorly supervised and wearisome duty[4,5,9]. It is an exceptional opportunity to learn to weigh evidence, to reach prompt, well thought out, decisions, and to perform – where necessary under active supervision – some particularly interesting and rewarding surgery:

(a) This must be seen to be a subject of major concern to senior staff; the planned increase in consultant numbers is highly relevant.
(b) Some basic trainees may need protection from excessive hours on duty, but higher surgical trainees, who need wide exposure to advanced emergency work, may need protection from too uniform an application of reduced hours of duty. In Denmark this lack of exposure has seriously affected experience among senior trainees[10].
(c) Many urgent operations for alimentary tract haemorrhage, for large bowel obstruction and perforation, and for vascular emergencies provide trainees with invaluable experience of the exercise of expert judgement and skill in the application of primary definitive major surgery.
(d) It should be a requirement for recognition for training that a hospital keeps an emergency theatre open throughout the day. Apart from reducing the need to operate at night, this allows most of these major procedures to be performed at a time which promotes both safety and learning[11].

Examination preparation. Preparation for the Royal College of Surgeons' fellowship examinations requires specific attention. The volume of on-call duties must allow for the study needed to understand the scientific basis of surgical practice. The educational value of clinical meetings needs promotion, and trainees need guidance over the preparation of presentations. Attendance should be the rule, with undue service demands checked by the keeping of a register of attendance, with results entered in log books. The present encouragement of the audit of each unit's work is very welcome for reasons (among others) well expressed by Dunphy: 'Two virtues of a surgeon, one essential and the other most becoming, are intellectual honesty and humility. Because so many decisions rest on probability, every untoward result must be critically reviewed'[12].

Critical review. The provision of regular unambiguous feedback is a consistent request from trainees. European junior hospital doctors, in a valuable report on graduate medical education, have stated that 'a critical review of the trainee's strengths and weaknesses is particularly necessary at the end of each association with a particular trainer. This in turn requires that trainers spend time observing the performance... of their trainees'[13].

Higher surgical training

The stage of promotion from basic to higher surgical training is necessarily a time of anxious competition. In the UK, this may be aggravated by the long overdue decision to relate the number of career registrars to those of senior registrars. It must be hoped that there will soon be a move to a single 6-year programme of higher training.

Future developments. How should higher surgical training take account of developments in general surgery in the 1990s? One guiding principle is that the majority of trainees go on to become general surgical consultants in district hospitals, where up to 40 per cent of patients arrive as an emergency, and the duty surgeon has to be ready to provide immediate care for the whole range of surgical illness and injury. At the same time, most surgeons in community hospitals now also pursue a special interest, and there is evidence that this benefits both the patients and the surgical teams. To encourage this development, higher trainees should be able to leave their training programme for a period to pursue their special interest on secondment to a unit in another region or country. There should also be much wider use of proleptic consultant appointments. This widens the field available to a hospital while allowing the chosen candidate to plan an educational programme appropriate to the needs of the vacancy.

Trends in surgery. Current trends in fibreoptic endoscopy and minimal access surgery will have a major influence on practice and therefore on training. Experience in gastrointestinal endoscopy is essential for district hospital surgeons, yet senior trainees report difficulty in securing training. Experience in the diagnostic use of the laparoscope can be extended; selective laparoscopy is, for instance, increasingly used in the management of women with acute abdominal pain, and trials show that this yields benefits to patients[14]. Elective operations on the stomach and duodenum and, for different reasons, on the biliary tract are becoming unusual in many centres. However, the Royal College of Surgeons of England has directed that 'laparoscopic surgery should be undertaken only by, or in the presence of, surgeons who are already fully trained in the conventional surgical procedure, and who have the experience to revert to standard techniques'[15]. Such experience is going to be difficult for our trainees to obtain. One answer may be to use minicholecystectomy, which is a valuable training operation which also offers advantages to patients[16]. Every advantage must be taken of gastric resections for cancer, and of emergency operations, to allow trainees to see open surgery of the upper abdominal organs.

Original investigation. New thought also needs to be devoted to the place assigned to original investigation in a training programme. At present a number of registrars prepare a thesis as 'a step towards promotion rather than a base for future investigative work, and this is not a good reason'[17]. It seems, indeed, to leave many with little interest in new ideas and further investigations. It would be a sound investment for the future of our National Health Service hospitals if a statutory study year were to be included in the 6 years of higher training. Full support would be given to those who wished to pursue a project in the laboratory. Others could combine attendance at a taught course (covering computer studies, data collection and analysis, and the methodology of audit and clinical investigation)[18] with preparation of an original indepth study. This might explore a problem area in management, or illustrate a clinical topic with a collection of reports of patients studied over the training years. These studies would be fully referenced and illustrated, and would be subjected to rigorous assessment. It would be appropriate for such a study, or published work, to become an element in the Intercollegiate Assessment.

The particular intention of this phase of training must be to leave trainees with a continuing attitude of open-mindedness towards the new ideas with which they will be confronted over the years. 'Training is directed towards learning to perform specific tasks: education prepares for the unexpected'[19].

The role of organization

Apprenticeship necessarily plays a large part in craft training, but, because it depends on the uncertainties of the one-to-one relationship already mentioned, it must be practised within a structured framework. The attention given to the supervision of training by the Royal Colleges has produced many improvements. The Royal Australasian College now has a requirement that each hospital with general surgical trainees must appoint a director of training. Apart from responsibility for the local programme, the director is required to submit a summary of every trainee's log book to the college office in Melbourne. There the figures are collated and national averages are calculated. If the returns of a hospital show that trainees are not receiving sufficient hands-on supervision over an adequate range of operations, a warning can be issued and the hospital will soon be visited.

There are advantages to a surgical division in having one of its number designated as director of training by a central authority:

(a) It enables the director to organize a training programme with the status necessary to ensure that teaching time is respected. Trainees have one person regularly available for advice.
(b) Financial and administrative pressures can lead to decisions being taken, such as closure of wards, which can have serious effects on training. It is then helpful for the director to be able to negotiate as the official representative of the central training authority.
(c) If such decisions are reflected in the log book figures forwarded to the central office by the director, it is preferable for there to be an impartial central committee which draws the attention of a hospital to the fact that its training figures continue to be unsatisfactory. In this situation everyone will be mindful that the surgical colleges have the power to withdraw recognition for training.
(d) The most important function of the director is to nurture, through example, a general recognition that enthusiasm for education is fundamental to the provision of a good service to patients.

In the final analysis, the vital element in training is the relationship between trainers and trainees because 'the example of the teacher is the most powerful influence on the standards of conduct and practice of the trainee'[20]. As mutual respect grows between teacher and pupil, many realize that what started as an educational relationship has developed into a productive and continuing friendship.

'The bottom line in surgical training must be to concentrate on the development of competence and compassion: everything else is second'[21].

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References

1. Tait L. Surgical training, surgical practice, surgical results. *Br Med J* 1890; **2**: 267–73.
2. Roberts J. The NHS observed. Junior doctors' years: training not education. *Br Med J* 1991; **302**: 225–8.
3. Nunn JN, Devlin HB. Lessons from the Confidential Enquiry into Perioperative Deaths in three NHS regions. *Lancet* 1987; **ii**: 1384–6.
4. Diggory RT. Training of surgical registrars: a regional audit. *Br Med J* 1988; **297**: 455–6.
5. Steele RJC, Logie JRC, Munro A. Technical training in surgery: the trainees' view. *Br J Surg* 1989; **76**: 1291–3.
6. Grant J, Marsden P, King RC. Senior house officers and their training: II. Perceptions of service and training. *Br Med J* 1990; **299**: 1265–8.
7. Fielding LP, Stewart-Brown S, Blesovsky L, Kearney G. Anastomotic integrity after operations for large-bowel cancer: a multi-centre study. *Br Med J* 1980; **281**: 411–14.
8. McArdle CS, Hole D. Impact of variability among surgeons on postoperative morbidity and mortality and ultimate survival. *Br Med J* 1991; **302**: 1501–5.
9. Kiff RS, Sykes PA. Surgery in a district general hospital. *J R Coll Surg Edinb* 1991; **36**: 45–7.
10. Hoffmann J, Fischer A. Juniors' hours. *Br Med J* 1990; **301**: 1159.
11. Commission on the Provision of Surgical Services. *Report of the Working Party on Consultant Responsibility in Invasive Surgical Procedures.* London: Royal College of Surgeons of England, 1990.
12. Dunphy JE. What puts the surge in surgery. *Aust NZ J Surg* 1974; **44**: 313–20.
13. Permanent Working Group of European Junior Hospital Doctors. Policy statement on postgraduate medical education. *Med Educ* 1989; **23**: 339–47.
14. Paterson-Brown S, Thompson JN, Eckersley JRT, Ponting GA, Dudley HAF. Which patients with suspected acute appendicitis should undergo laparoscopy? *Br Med J* 1988; **296**: 1363–4.
15. Royal College of Surgeons of England. *Memorandum on Minimal Access Surgery.* London: RCS, 1990.
16. Cheslyn-Curtis S, Russell RCG. Laparoscopic cholecystectomy. *Br Med J* 1991; **302**: 594.
17. Forrest APM. Evolution of academic surgery. *Br Med J* 1989; **299**: 1552–4.
18. Farndon JR. Correspondence. *Ann R Coll Surg Engl* 1991; **73**(Suppl 1): 5–6.
19. Fraser RC. Undergraduate medical education: present state and future needs. *Br Med J* 1991; **303**: 41–3.
20. General Medical Council. *Recommendations on the Training of Specialists.* London: GMC, 1987.
21. O'Neill JA. Pediatric surgery: whither goest thou? *J Pediatr Surg* 1990; **25**: 2–10.

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Seton treatment of high anal fistulae

Seventy-four patients who underwent seton treatment of high anal fistulae over a 6-year period have been reviewed. Four different techniques were used: staged fistulotomy (n = *24*), *cutting seton* (n = *13*), *short-term seton drainage* (n = *14*) *and long-term seton drainage in patients with Crohn's disease* (n = *23*). *Recurrence developed in two patients (8 per cent) undergoing two-stage fistulotomy; two patients (14 per cent) undergoing short-term drainage and nine (39 per cent) of the patients with Crohn's disease. Three patients with Crohn's disease required proctectomy for progressive perianal disease. The remaining 11 patients with Crohn's disease (48 per cent) obtained a good result. None of the patients treated with a cutting seton developed a recurrence. Minor incontinence developed in 13 patients (54 per cent) undergoing two-stage fistulotomy and seven patients (54 per cent) treated with a cutting seton. When sphincter muscle was not divided, five patients (36 per cent) undergoing short-term drainage and six patients (26 per cent) undergoing long-term drainage developed minor incontinence. High complex fistulae can be successfully treated with only minor loss of continence using different seton techniques. In high Crohn's fistulae, long-term seton drainage preserves sphincter function, but recurrence is common if the seton is removed.*

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The object of surgical treatment of an anal fistula is to eradicate it without disturbing anal continence. These goals can be achieved by laying open an intersphincteric or low trans-sphincteric fistula[1,2]. However, laying open a high trans-sphincteric, suprasphincteric or extrasphincteric fistula involves division of most, or all, of the sphincter muscle, which would compromise continence. A variety of techniques have been described to treat high fistulae which preserve the anorectal ring and sphincter. These include the Parks' fistulotomy[3], rerouting the fistula tract[4], closing the internal opening[5], using endorectal advancement flaps[6–9], fistulotomy with primary repair of the sphincter[10] and insertion of a seton[11–18]. Of these techniques, we have mainly chosen to use a seton. The aim of this study was to assess the results of seton treatment of high fistulae with particular reference to recurrence rates and postoperative continence.

Patients and methods

Seventy-four patients (45 men, 29 women) underwent surgical treatment of anal fistula using a seton at the University of Minnesota and affiliated hospitals between July 1984 and July 1990. The age of the patients ranged from 29 to 74 years (median 42 years). During the same period, 739 other patients underwent primary fistulotomy for low anal fistulae.

Twenty-three patients had Crohn's disease. The length of history of perianal involvement ranged from 3 months to 10 years (median 2 years). At the time of surgery, eight patients had no evidence of active intestinal disease. Six patients had rectal disease, ten had colonic disease and eight had small bowel disease (seven patients had two or three sites affected). Eighteen of the patients with Crohn's disease (78 per cent) had undergone previous drainage of an abscess on one to five occasions; two had undergone dilatation of an anorectal stricture, and defunctioning colostomy had been performed in one patient. Only three patients with Crohn's disease had not undergone previous anorectal surgery. Of the 51 patients without Crohn's disease, 27 (53 per cent) had undergone previous drainage of a perianal abscess. A further eight patients had undergone previous fistula surgery where a portion of the sphincter muscle was divided.

Fistulae were classified by the method of Parks *et al.*[19]. Sixty-one fistulae were trans-sphincteric, passing deep to over 50 per cent of the external sphincter muscle; 13 were thought to be suprasphincteric, passing deep to all the sphincter muscle. Surgery was performed under general or regional anaesthesia in the prone jack-knife position. The external opening of the tract was gently probed and the external tract and any side tracts opened. The tract through the sphincter and the internal opening were identified by gentle probing from both sides. The anoderm overlying the internal opening was excised and an internal sphincterotomy was performed distally to open the intersphincteric space, in an attempt to eradicate the cryptoglandular origin of the fistula. The skin edges of the external wounds were marsupialized with 3/0 chromic catgut. Wounds were dressed with fluffed gauze; anal packing was not used. Four different seton techniques were used.

Two-stage fistulotomy (n = *24*)

A large (no. 1) silk suture was passed along the tract and tied loosely over the sphincter and healing of the external wounds monitored. The second stage was performed 4–8 weeks later, when the seton was removed and the enclosed sphincter muscle was divided, laying open the residual fistula tract.

Cutting seton (n = *13*)

A large silk suture or elastic band was passed along the tract and tied snugly around the sphincter muscle. The patient was followed regularly and the seton tightened as necessary – a simple method of doing this was to apply a Barron band ligature to the stretched elastic band. In this way the seton gradually divided the anal sphincter.

Short-term seton drainage (n = *14*)

A large silk suture or fine plastic feeding tube (7 Fr) was passed along the tract and tied loosely over the external sphincter. The patient was followed until all external wounds had healed leaving only the deep fistula tract containing the seton. The seton was then removed and the patient followed until the tract healed.

Long-term seton drainage (n = *23*)

This technique was used exclusively in patients with Crohn's disease. These fistulae often had multiple, complex external tracts, which were laid open. A plastic or Silastic® (Dow Corning, Reading, UK) feeding tube was passed along the tract and loosely tied. Anoderm and skin overlying the sphincter muscle were not excised and the intersphincteric space was not drained as it was often doubtful that these fistulae arose from a cryptoglandular infection. The aim was to leave the seton in place for prolonged periods of time (months or years) to act as a long-term drain and prevent further suppuration. Occasionally seton replacement was required.

Patients were followed regularly until all wounds healed. Patients

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Table 1 *Healing of wounds and recurrence of fistulae*

Method used	Healing time (weeks)*	Recurrence†
Two-stage fistulotomy ($n = 24$)	17 (10–40)	2 (8)
Cutting seton ($n = 13$)	16 (8–36)	0
Short-term seton ($n = 14$)	10 (4–34)	2 (14)
Long-term seton (Crohn's) ($n = 23$)	Not applicable	9 (39)

Values given are * median (range); † number of patients (percentage)

with long-term setons were evaluated every 3–6 months. Follow-up range was 4–60 months (median 24 months). Time for wound healing was documented in the notes. A recurrence was defined as a discharge or an abscess developing in the same region as the original fistula. Patients were questioned about the effect of surgery on faecal continence. Major incontinence was defined as any episode of loss of formed stool or persistent incontinence of liquid stool. Minor incontinence was defined as persistent loss of control of flatus or episodic loss of liquid stool occurring more than 4 weeks after surgery.

Results

Non-Crohn's fistulae

All fistula wounds eventually healed. Healing was quickest after removal of a short-term drainage seton (*Table 1*). Two patients (8 per cent) developed recurrent perianal suppuration in the region of the original fistula after two-stage fistulotomy; in both patients, simple drainage alone was performed. No further abscesses have developed after 3 and 16 months. Recurrence was higher after short-term seton drainage; two of the 14 patients (14 per cent) developed recurrent suppuration. Simple drainage was performed in one patient and a fistula tract was laid open in the second. No further recurrence has occurred after 8 and 18 months. None of the 13 patients treated by a cutting seton has developed recurrent perianal suppuration.

The effect of surgery on continence is shown in *Table 2*. Minor incontinence was more frequent in the two groups where sphincter muscle was divided than in the patients who underwent drainage without division of muscle. All patients reported that incontinence improved within 1 year of surgery to the extent that it no longer bothered them, although some still wore a pad for security. Six of the eight patients who had undergone previous fistula surgery where muscle was divided developed transient incontinence, compared with 15 of 27 who had undergone abscess drainage alone and six of 16 who had had no previous perianal surgery.

Crohn's fistulae

A good result with long-term seton drainage was obtained in 11 (48 per cent) patients. In three of these, the seton was removed after all other wounds had healed and the fistula tract closed without further problems for 1, 1·5 and 3 years. In the other eight, the fistula tract remained quiescent without abscess, but did not close, for between 6 months and 5 years. In these patients the seton remained in place for between 10 weeks and 2·5 years, and two patients eventually required proctocolectomy for severe colonic disease. Nine patients developed recurrent fistulous abscess 6 months to 3·5 years after initial treatment, in all of whom the seton had fallen out or had been removed. Recurrent fistulae were treated by the same technique and a new seton was inserted. In three patients seton treatment failed and proctectomy was required because of progressive perianal and rectal Crohn's disease.

Six patients reported minor incontinence (*Table 2*); one patient had minor incontinence before surgery and four had undergone extensive ileal and colonic resections resulting in loose stools. A further three patients reported full anal continence but experienced episodic discharge of mucus and gas through the residual fistula tract. The remaining patients did not notice any change in continence after seton insertion.

Discussion

Operation for anal fistula is among the oldest surgical procedures, the use of a seton to treat an anal fistula being described by Hippocrates[20]. The word seton is derived from the Latin *seta*, a bristle. Many different materials have been used as a seton, including silk, wire, elastic band, Penrose drain and nylon and plastic tubing[11–18].

A seton has a number of uses in fistula surgery. First, a loosely tied thread through the fistula tract may act as a marker of the level of the internal opening and tract when the patient is examined after operation[21] and may be a useful guide to whether the fistula can be safely laid open[22]. Secondly, the seton can be used to treat the fistula (as in the present series). The seton is thought to stimulate fibrosis which fixes the sphincter muscle and prevents wide separation of the ends when the muscle is divided at a second stage[11,14], although this theory has been challenged[22]. Thirdly, it can be used to cut through the muscle by gradually tightening the ligature or elastic band[12,16]. Fourthly, it can function as a drain to prevent recurrent suppuration while the external wounds heal; the seton is then removed, allowing the tract to close[13]. Finally, in Crohn's disease, where there is a high risk of recurrent sepsis, it can be left in place for prolonged periods. It is difficult to be dogmatic as to when to apply each technique. The authors' preference is to use a cutting seton when not all the sphincter is involved and a drainage seton if the fistula passes deep to all, or nearly all, of the sphincter.

This series shows that difficult, high trans-sphincteric and suprasphincteric fistulae can be treated successfully by a seton. The results presented compare favourably with those of other authors (*Table 3*). Recurrence rates in our series were highest when the seton was simply removed, especially in Crohn's disease, which is not surprising as the internal opening of the fistula has not been eradicated. A high incidence of persistent or recurrent fistulae after removal of a drainage seton has been noted in other series[17,18]. Thomson and Ross[17] performed a second-stage fistulotomy if the fistula persisted after seton removal, which invariably eradicated the fistula.

Seton fistulotomy, either performed in two stages or using the seton to cut through the sphincter muscle, cured all but two of the 37 fistulae so treated. Similar high success rates have been obtained by other groups[13,16,17]. Ramanujam *et al.*[14] reported excellent results using a modified two-stage technique: partial proximal sphincterotomy was performed at the first stage and the distal sphincterotomy completed at a second stage. Setons have also been used successfully to treat extrasphincteric fistulae[15].

Incontinence after fistula surgery is difficult to quantitate. Most patients experience some minor loss of control in the postoperative period and we warn our patients to expect this. Simple laying open of low anal fistulae is associated with disturbance in faecal continence in up to 34 per cent of patients[1,23]. Ramanujam *et al.*[14] noted that all 45 of their patients lost control of flatus after operation, but this persisted in only one.

In the present series, three patients reported major incontinence following surgery; this resolved with time. Minor incontinence was more frequent when sphincter muscle was divided, either at a second stage or using a cutting seton.

Table 2 *Effect of surgery on continence*

Method used	Incontinence Major*	Incontinence Minor
Two-stage fistulotomy ($n = 24$)	1 (4)	13 (54)
Cutting seton ($n = 13$)	1 (8)	7 (54)
Short-term seton ($n = 14$)	1 (7)	5 (36)
Long-term seton (Crohn's) ($n = 23$)	0	6 (26)

Numbers in parentheses are percentages. *Resolved with time

Table 3 *Results of treatment compared with previous studies*

Author	Material	Method	Number of patients	Recurrence	Incontinence*	
					Major	Minor
Parks and Stitz[13]	Nylon	Drainage	50	5 (10)	0	– (17)
Parks and Stitz[13]	Nylon	Two-stage fistulotomy	30	1 (3)	0	– (39)
Ramanujam *et al.*[14]	Mersilene®	Two-stage fistulotomy	45	1 (2)	0	1 (2)
Culp[16]	Penrose	Cutting	20	0	0	3 (15)
Thomson and Ross[17]	Nylon	Drainage	34	19 (56)†	0	2 (6)
Thomson and Ross[17]	Nylon	Two-stage fistulotomy	19	0	3 (16)	10 (53)
Kennedy and Zegarra[18]	Silk	Drainage	32	7 (22)†	0	7 (22)

* Continence was not assessed in all patients studied. † Fistulae that did not heal were treated by second-stage fistulotomy. Numbers in parentheses are percentages

Patients who had undergone previous fistula surgery were more likely to experience incontinence after seton treatment than those who underwent simple abscess drainage or who had not undergone previous surgery. Sainio and Husa[23] also noted that previous fistula surgery was associated with greater risk of developing postoperative incontinence.

Similar rates of incontinence have been reported by other groups (*Table 3*). Thomson and Ross[17] reported major incontinence in three of 16 patients undergoing second-stage fistulotomy, all of whom required surgical repair of the anal sphincter. Minor incontinence was reported by 17 per cent of patients treated by drainage seton compared with 62 per cent of patients who underwent two-stage fistulotomy. Parks and Stitz[13] also noted a higher rate of incontinence after two-stage fistulotomy than after drainage alone. Manometric studies have shown that patients who experience postoperative incontinence have lower resting and squeeze pressures than patients with normal control[24]. Belliveau *et al.*[25] showed a fall in resting pressure in the lower anal canal after treatment of intersphincteric, trans-sphincteric and suprasphincteric fistulae. Furthermore, postoperative resting pressure and maximum voluntary contraction pressures were significantly lower in patients with trans-sphincteric fistulae treated by muscle division than in patients with trans-sphincteric or suprasphincteric fistulae treated without muscle division using a drainage seton. The lower sphincter pressure was associated with a higher incidence of incontinence in the patients treated by sphincter division.

Treatment of high fistulae by mucosal advancement flap is also associated with low recurrence rates[6–9]. Wedell *et al.*[7] treated 30 fistulae by advancement flap, with only one recurrence and no alteration in continence. Aguilar *et al.*[6] reported a recurrence rate of 2 per cent in 150 patients, with 15 patients (10 per cent) reporting minor incontinence. However, they did not detail the level of fistula treated. These results are comparable with those from seton treatment, which is simpler to perform.

In conclusion, a seton can be used in a number of ways to treat high, complex, anal fistulae. Recurrence rates are low after definitive treatment and disturbance in continence is minor. The results are similar to those obtained using more complex methods of treating these difficult fistulae.

References

1. Shouler PJ, Grimley RP, Keighley MRB, Alexander Williams J. Fistula-in-ano is usually simple to manage surgically. *Int J Colorect Dis* 1986; **1**: 113–15.
2. Vasilevsky C-A, Gordon PH. Results of treatment of fistula-in-ano. *Dis Colon Rectum* 1984; **28**: 225–31.
3. Parks AG. Pathogenesis and treatment of fistula-in-ano. *Br Med J* 1961; **i**: 463–9.
4. Mann CV, Clifton MA. Re-routing the track for the treatment of high anal and anorectal fistulae. *Br J Surg* 1985; **72**: 134–7.
5. Reznick RK, Bailey HR. Closure of the internal opening for treatment of complex fistula-in-ano. *Dis Colon Rectum* 1988; **31**: 116–18.
6. Aguilar PS, Plasencia G, Hardy TG *et al.* Mucosal advancement in the treatment of anal fistula. *Dis Colon Rectum* 1985; **28**: 496–8.
7. Wedell J, Meir zu Eissen P, Banzhaf G, Klein L. Sliding flap advancement for the treatment of high level fistulae. *Br J Surg* 1987; **74**: 390–1.
8. Jones IT, Fazio VW, Jagelman DG. The use of transanal rectal advancement flaps in the management of fistulas involving the anorectum. *Dis Colon Rectum* 1987; **30**: 919–23.
9. Shemesh EI, Kodner IJ, Fry RD, Neufeld DM. Endorectal sliding flap repair of complicated anterior anoperineal fistulas. *Dis Colon Rectum* 1988; **31**: 22–4.
10. Parkash S, Lakshmiratan V, Gajendran V. Fistula-in-ano: treatment by fistulectomy, primary closure and reconstruction. *Aust NZ J Surg* 1985; **55**: 23–7.
11. Allen JH, Haskell B. A two stage operation for fistula-in-ano. *Surg Gynecol Obstet* 1934; **58**: 651–4.
12. Hanley PH. Rubber band seton in the management of abscess-anal fistula. *Ann Surg* 1978; **187**: 435–7.
13. Parks AG, Stitz RW. The treatment of high fistula-in-ano. *Dis Colon Rectum* 1976; **19**: 487–99.
14. Ramanujam PS, Prasad ML, Abcarian H. The role of seton in fistulotomy of the anus. *Surg Gynecol Obstet* 1983; **157**: 419–22.
15. Kuypers HC. Use of the seton in the treatment of extrasphincteric anal fistula. *Dis Colon Rectum* 1984; **27**: 109–10.
16. Culp CE. Use of Penrose drains to treat certain anal fistulas: a primary operative seton. *Mayo Clin Proc* 1984; **59**: 613–17.
17. Thomson JPS, Ross AHMcL. Can the external anal sphincter be preserved in the treatment of trans-sphincteric fistula-in-ano? *Int J Colorect Dis* 1989; **4**: 247–50.
18. Kennedy HL, Zegarra JP. Fistulotomy without external sphincter division for high anal fistulae. *Br J Surg* 1990; **77**: 898–901.
19. Parks AG, Gordon PH, Hardcastle JD. A classification of fistula-in-ano. *Br J Surg* 1976; **63**: 1–12.
20. Adams F. On fistulae. In: Adams F, ed. *The Genuine Work of Hippocrates*. Baltimore: Williams and Wilkins, 1939: 337–42.
21. Goligher JC. Fistula-in-ano. In: *Surgery of the Anus, Rectum and Colon*. 5th ed. London: Baillière Tindall, 1984: 178–220.
22. Hawley PR. Anorectal fistula. *Clin Gastroenterol* 1975; **4**: 635–49.
23. Sainio P, Husa A. Fistula-in-ano. Clinical features and long-term results of surgery in 199 adults. *Acta Chir Scand* 1985; **151**: 169–76.
24. Sainio P. A manometric study of anorectal function after surgery for anal fistula, with special reference to incontinence. *Acta Chir Scand* 1985; **151**: 695–700.
25. Belliveau P, Thomson JPS, Parks AG. Fistula-in-ano. A manometric study. *Dis Colon Rectum* 1983; **26**: 152–4.

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Frequency of familial colorectal cancer

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Familial clustering of cancer is not uncommon. The frequency of familial colorectal cancer was estimated by taking family histories from 100 patients presenting with apparently sporadic colorectal cancer. Compared with controls, the relative risk of a positive family history for colorectal cancer was 4·6. Life-table methods were used to examine the observed to expected mortality from colorectal cancer. Overall there was a fourfold increase in mortality rate ($P<0.0001$)*, which was greatest in female relatives of patients with colonic cancer* ($P<0.001$)*. Three families with dominant inheritance of colorectal cancer and one family with Lynch type II syndrome were identified. Nine per cent of patients had siblings who had developed colorectal cancer a median of 4 years before the diagnosis of the index patient (range 1–17 years). It is recommended that a careful family history should be obtained from all patients with colorectal cancer. Where a positive history is obtained a geneticist may determine empirical risks for the development of colorectal cancer and the appropriate method of surveillance may be selected.*

In 1988, in England and Wales, there were nearly 17 000 deaths from colorectal cancer[1]. The natural history of the disease and the diagnostic methods fulfil many of the criteria required of a screening programme. Screening of asymptomatic individuals using faecal occult blood tests has had a disappointing compliance rate[2].

Strategies aimed at the early detection of colorectal cancer in high-risk groups form part of the clinical management of patients with conditions such as long-standing inflammatory bowel disease and adenomatous polyposis coli. Screening the immediate family of patients with adenomatous polyposis coli has become routine clinical practice and the identification of an affected individual mandates the offer of a prophylactic colectomy. In contrast the screening for dysplasia and cancer in patients with ulcerative colitis is part of routine clinical practice but the 'costs' of screening possibly outweigh the 'benefits'[3].

The clustering of cancer in certain families is well recognized. In 1904, Watkins[4] described a family with a high incidence of colorectal cancer and pondered 'the question of the inheritance of cancer'. Warthin[5] analysed the families of 1000 patients with several types of histologically verified cancer and is credited as being the first to suggest that the incidence of malignant tumours in these families might be due to an inherited susceptibility to cancer. Woolf[6] analysed the death certificates of relatives of patients with colorectal cancer and concluded that there was a genetic component to the disease, noting that first-degree relatives of patients dying from cancer of the colon or rectum had a threefold increased risk of developing colorectal cancer compared with the general population.

The principal aim of this study was to establish the incidence of colorectal cancer in the first-degree relatives of patients presenting with colorectal cancer to one consultant surgeon (P.J.F.) and to establish the feasibility of offering screening to the remaining first-degree relatives.

Patients and methods

During an outpatient visit all patients who had undergone treatment for primary colorectal cancer were invited to give a family history to identify first-degree relatives (parents, siblings and children) for screening. The family history of a deceased index case was obtained from the spouse and confirmed by a first-degree relative before inclusion in the study. The detailed interview usually took place in the patient's own home and was taken by B.M.S. or F.G. The age and cause of death in relatives was verified, where possible, by reference to hospital pathology records, death certificates or from regional cancer registries.

Particular care was taken to avoid biased selection of cases and no referrals had occurred as a consequence of a family history of colorectal cancer. Patients with a history of adenomatous polyposis coli were excluded. In all, 124 consecutive patients were contacted of whom nine refused to give details of their family. Patients who were unable to give a full family history or who were unsure as to the age and cause of death in their first-degree relatives were excluded ($n=15$). The results of the first 100 complete family histories are presented. As a control group, family histories were taken from age- and sex-matched individuals with various non-malignant conditions.

Tables from the Office of Population Censuses and Surveys (OPCS) for 1988 were used to calculate the expected number of deaths among first-degree relatives in 10-year age groups[1]. Each first-degree relative contributes 'years at risk' only to the decades through which they have lived. The expected incidence of colorectal cancer is low in the early decades and higher later in life. Only those relatives living through later decades provide 'years at risk' during which there is a significant incidence of colorectal cancer. This type of analysis eliminates the problem of individuals having different numbers of relatives and controls for their ages. The Poisson distribution was used to examine the significance of any difference between the observed and expected number of deaths.

Results

The 100 index patients were aged from 36 to 89 years (mean 71 years) with an equal male:female ratio. Eighty-six were elective patients and 14 presented as emergencies. The most frequent site of cancer was the rectum and rectosigmoid (45 patients). There were 23 caecal and right colonic tumours, a distribution expected in an unselected population.

Twenty-three of the index cases gave a history of colorectal cancer in a first-degree relative compared with only five in the control group (relative risk for a positive family history of 4·6). There was no difference in the incidence of any other common type of malignancy (*Table 1*). There was no significant difference in the age, site or the Dukes' classification of the cancer in the patients with a family history compared with the remaining patients with no family history.

Of the 23 index cases with a positive family history, the death in first-degree relatives was confirmed in only 20 (relative

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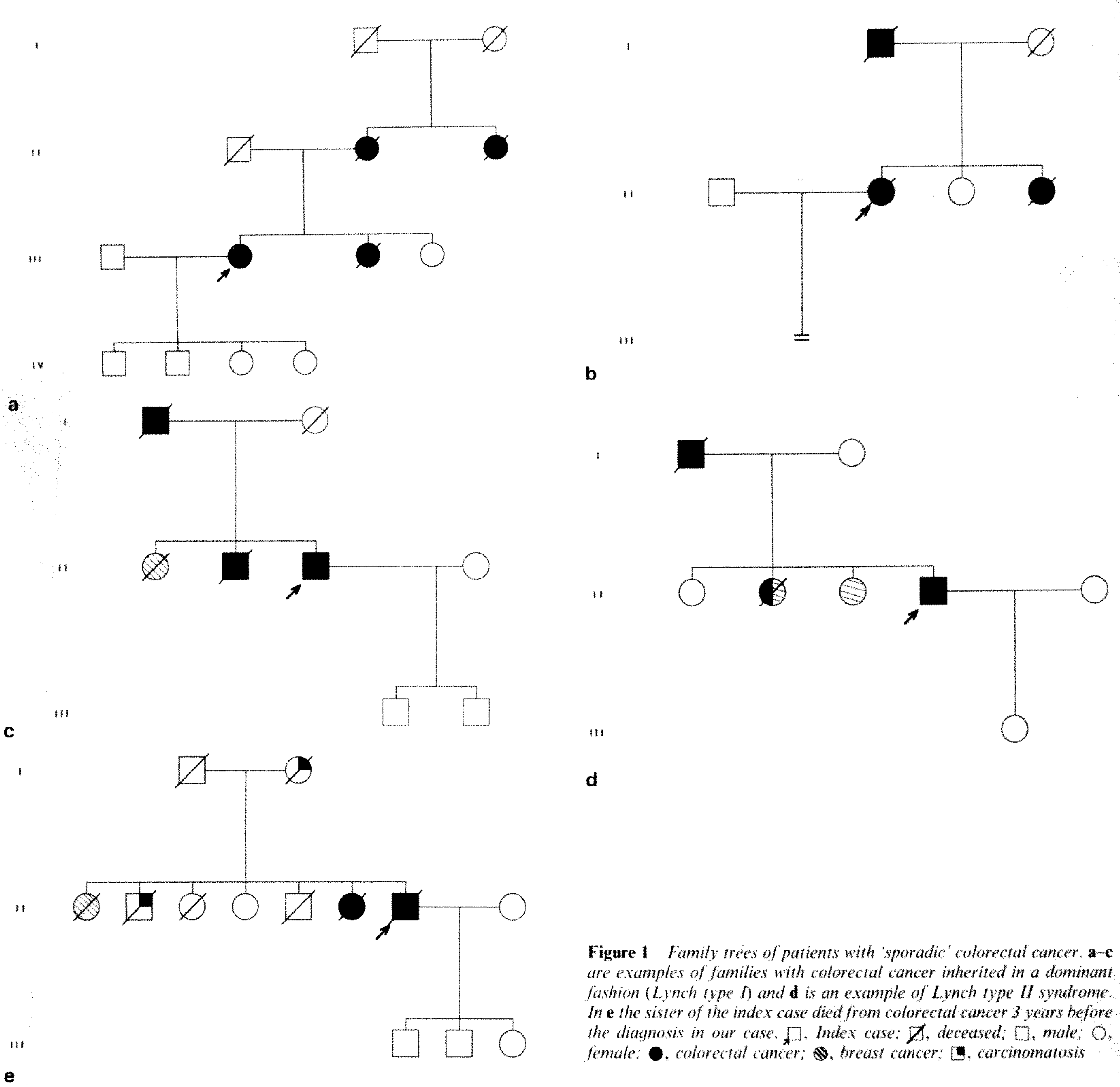

Figure 1 *Family trees of patients with 'sporadic' colorectal cancer.* **a–c** *are examples of families with colorectal cancer inherited in a dominant fashion (Lynch type I) and* **d** *is an example of Lynch type II syndrome. In* **e** *the sister of the index case died from colorectal cancer 3 years before the diagnosis in our case.* ↗□, *Index case;* ⧄, *deceased;* □, *male;* ○, *female;* ●, *colorectal cancer;* ▨, *breast cancer;* ◪, *carcinomatosis*

risk for a positive family history of 4). In two patients the cause of death of the parent alleged to have died from colorectal cancer between 30 and 50 years ago could not be traced, and one index patient's brother died from gastric cancer when it was alleged that he had died from colorectal cancer. The 20 confirmed families had 23 first-degree relatives with confirmed colorectal cancer. There were three families with colorectal cancer inherited in a dominant fashion (defined as at least three first-degree relatives with colorectal cancer) (*Figure 1a–c*) and one family with Lynch type II syndrome (three first-degree relatives with colorectal cancer and other adenocarcinomas (breast, ovarian and endometrial)) (*Figure 1d*). Nine patients with a confirmed family history of colorectal cancer had siblings who had developed colorectal cancer a median of 4 years before the diagnosis of the index patient (range 1–17 years), as illustrated by *Figure 1e*.

As the mortality statistics from the OPCS rely upon the diagnosis of colorectal cancer appearing on the death certificate, only those cases confirmed by death certificates were valid when used in the life-table analysis. Of the 23 first-degree relatives from the 20 families, 18 were confirmed by death certificates. The 100 index patients had 840 first-degree relatives from which calculation of the number of years at risk, in 10-year age groups, was made. This allowed the analysis of the observed to expected incidence of colorectal cancer from the OPCS statistics. There were 18 observed deaths from colorectal cancer in the first-degree relatives compared with an expected incidence of 4·11 (observed:expected ratio of 4·38; $P < 0.0001$, Poisson distribution) (*Table 2*). The mortality rate varied with the site of the cancer in the index case, being greatest for female relatives of patients with colonic rather than rectal cancer ($P < 0.001$).

If the diagnosis could not be confirmed by other means,

Table 1 *Family history of cancer in first-degree relatives*

	Relatives of patients	Relatives of controls
Breast	10	8
Oesophagus	0	1
Stomach	10	10
Colorectum	23	5*
Uterus	3	4
Ovary	1	2

Only the most common cancers are listed; * relative risk for a positive family history of 4·6 death certificates were obtained for those deaths stated to have been from any type of cancer. In all but one instance cause of death in relatives suspected to have died from colorectal cancer was confirmed. One index patient stated that the relative had died from liver cancer whereas the death certificate showed the cause of death to be colorectal cancer. Excluding the cases for which we were unable to obtain a death certificate, a history of colorectal cancer in a first-degree relative was verifiably dependable (sensitivity 96 per cent).

Assuming screening protocols can be based upon a family history and calculation of empirical risk values for the development of colorectal cancer[7], then this series of patients yielded 127 first-degree relatives aged between 50 and 75 years who might benefit from some form of screening (risk of one in 17). Fifteen per cent of the patients had no living first-degree relatives and the relatives of 14 per cent of the patients did not lie within the above age group. In addition to the 127, there were 36 first-degree relatives whose risk was calculated, based upon the family tree, to be one in ten or more, perhaps warranting more intensive approaches to screening for colorectal neoplasia[7].

Discussion

The dominantly inherited non-polyposis colorectal cancer syndromes (HNPCC or Lynch syndrome types I and II) are four to five times more frequent than adenomatous polyposis coli[8], and strategies for their management are now well established[7–9]. Mecklin[10] estimated that adenomatous polyposis coli and HNPCC account for between 4 and 6 per cent of cases of colorectal cancer. Of the remaining cases, 10–20 per cent are familial, in that the patients with colorectal cancer have one or more first-degree relatives who are similarly affected, but with no discernible pattern of inheritance[10,11]. Lifetime risks for the development of colorectal cancer can be estimated: one in 17 for individuals with one first-degree relative affected, rising to one in six when two first-degree relatives are affected[7,12].

In this study 23 per cent of patients with apparently sporadic disease presenting to one general surgeon gave a history of colorectal cancer in a first-degree relative, a finding in agreement with studies from London[12], France[13] and northern Italy[14]. The family history could be confirmed in only 20 of these families, giving a relative risk for a positive history of four when compared with controls. Four families with HNPCC were identified, three with Lynch type I syndrome ('site specific' HNPCC) and one with Lynch type II syndrome. The 20 families had 23 relatives reported to have died from colorectal cancer, of which 18 were confirmed by death certificates. The family history of colorectal cancer was verified in all these 23 relatives and there was only one index case in which it was suggested that a first-degree relative had died from colorectal cancer when this was not the case. In the two index cases for which no evidence was obtained, comments such as 'my father died from a blockage of the bowel' suggest that colorectal cancer may have contributed to the relative's death. In only one instance was the death certificate found to list colorectal cancer as the cause of death in a relative in whom it was not suspected, and the patient presumably died from metastatic colorectal cancer to the liver. These findings suggest that people usually recall the cause of death of their close relatives accurately and that empirical risks to individuals of developing colorectal cancer can be reliably given based upon the family tree alone.

Previous studies[6,12–17] found similar ratios for a positive family history in patients with colorectal cancer as reviewed by Bishop and Burt[18] (*Table 3*). Although the relative risk for a positive family history differs widely there is a consistent threefold to fourfold increased incidence of colorectal cancer in relatives of patients with sporadic colorectal cancer. This increased risk is also present in individuals whose only risk factor is that they are closely related to patients with benign adenomatous polyps[13–15] (*Table 3*). There are, however, a number of problems with performing case–control studies including ascertainment bias. To avoid this the mortality rate from colorectal cancer in the first-degree relatives ($n = 840$) was compared with that which was to be expected using mortality statistics from the OPCS[1]. There was a fourfold increase ($P < 0{\cdot}0001$) in the observed to expected mortality rate from colorectal cancer in the first-degree relatives, in agreement with Lovett[12]. In addition, although our numbers are small, the site of the cancer in our patients, but not their sex, appeared to influence the mortality rate from colorectal cancer in the first-degree relatives; the mortality rate was greatest among female relatives of patients with colonic cancer ($P < 0{\cdot}001$).

To date there have been several reports[19–29] concerning screening of this 'high-risk' group. Some of these studies have been uncontrolled and retrospective (*Table 4*). Debate has centred around the choice of flexible sigmoidoscopy or colonoscopy as the most appropriate screening method[30,31]. Colonoscopy is the more sensitive method for detecting

Table 2 *Mortality from colorectal cancer in first-degree relatives of index patients with colorectal cancer*

	Observed	Expected*	Ratio	*P*†
Men	6	2·14	2·8	0·02
Women	12	1·97	6·1	0·001

* Expected figures are derived from Office of Population Censuses and Surveys tables, based upon years at risk for 840 first-degree relatives; † significance of difference from expected (Poisson distribution)

Table 3 *Relative risk of a positive family history of colorectal cancer in patients with colorectal neoplasia (cancer or adenomatous polyp)*

	Frequency of family history of colorectal cancer				
		Patients with colorectal cancer		Patients with adenomatous polyp	
Reference	Controls (%)	%	Relative risk	%	Relative risk
Woolf[6]*			**3·3**		
Macklin[16]*			**3·2**		
Lovett[12]†			**3·5**		
Duncan and Kyle[17]	2·0	16	**8·0**		
Maire *et al.*[13]	3·5	19	**5·3**	14·7	**4·2**
Ponz de Leon *et al.*[14]	5·4	20·9	**3·9**	18·5	**3·4**
Bonelli *et al.*[15]	5·1	11·3	**2·4**	14·5	**3·2**
Present study	5·0	23	**4·6**		

* These studies used archival death registers; † results compared with mortality statistics. Relative risk is determined by comparing the frequency of a positive family history in patient groups and controls. Table based on Reference 18, with permission from S. Karger AG, Basel, Switzerland

Table 4 *Incidence of colorectal neoplasia in first-degree relatives of patients with colorectal cancer*

	Group	Mean age (years)	Sample size	Screening method	Incidence of neoplasia (%)	Neoplasia >55 cm (%)	Type of study
Gryska and Cohen[19]	Relatives	54	49	Colonoscopy	63*	14†	Retrospective
Rosen *et al.*[20]	Relatives	46	471	FOBT/FS	8	Not stated	Prospective
	Controls	57	457	FOBT/FS	4	Not stated	
Cannon-Albright *et al.*[21]	Relatives	51	407	FS	19	Not stated	Prospective
	Controls	52	265	FS	12	Not stated	
Guillem *et al.*[22]	Relatives	Not stated	48	Colonoscopy	25	8	Retrospective
Grossman and Milos[23]	Relatives	54	154	Colonoscopy	18	8	Prospective
Guillem *et al.*[24]	Relatives	50	128	Colonoscopy	12	Not stated	Prospective
	Controls	54	49	Colonoscopy	8	Not stated	
McConnell *et al.*[25]	Relatives	Not stated	125	Colonoscopy	12	5	Prospective
McConnell[26]	Relatives	Not stated	255	Colonoscopy	Not stated	3	Prospective
Orrom *et al.*[27]	Relatives	51	114	Colonoscopy	20	5	Prospective
Baker *et al.*[28]	Relatives	55	201	Colonoscopy	27	12	Retrospective
Herrera *et al.*[29]	Relatives	Not stated	200	FOBT/FS	9	9‡	Retrospective

* Incidence of adenomas not given, percentage relates to 'polyps'; † 40 cm used as criterion for cut-off; ‡ based on 87 colonoscopies. FOBT, faecal occult blood test; FS, flexible sigmoidoscopy

adenomatous polyps proximal to the splenic flexure and it is the investigation of choice when screening individuals from families with HNPCC[7–11]. Colonoscopy may be the method of choice when screening individuals who have two first-degree relatives with colorectal cancer where the lifetime risk has been calculated to be one in six[7]. It can be seen from *Table 4* that only 7 per cent of screened relatives have neoplasia beyond the reach of the 60-cm flexible sigmoidoscope, an examination that can usually be performed in the outpatient department with little discomfort.

Screening first-degree relatives with a risk of less than one in ten by colonoscopy would impose an impossible burden on the resources currently available in the UK. Flexible sigmoidoscopy may be adequate, and if adenomatous polyps are discovered then full colonoscopy is merited to detect and treat more proximal pathology. Based on this series of 100 patients, and assuming full compliance, the finding of neoplasia in 10 per cent of relatives undergoing flexible sigmoidoscopy would involve performing 127 flexible sigmoidoscopies and 13 colonoscopies. In relatives with risk values of one in ten or more[7], colonoscopic investigation is warranted, and from our data this would involve a further 36 examinations. On balance, of 100 patients with 'sporadic' colorectal cancer, a third have no relatives to screen and two-thirds of the workload generated by screening the first-degree relatives of the remaining patients could be accomplished by flexible sigmoidoscopy alone.

Because the majority of, if not all, colorectal cancers arise in 'benign' adenomatous polyps[32], and screen-detected cancers are generally found at a more favourable pathological stage[2,33], screening protocols for high-risk groups in the general population should be considered. At least nine cancers in this study might have been detected earlier if screening had followed the diagnosis in their younger siblings. Eddy *et al.*[34] have estimated mathematically that screening this high-risk population by flexible sigmoidoscopy, followed by colonoscopy when appropriate, could reduce the colorectal cancer mortality rate by up to 85 per cent, and that screening by annual faecal occult blood test would, at best, reduce the mortality rate by no more than 25 per cent.

It has been suggested that the number of individuals with a gene for susceptibility to colonic neoplasia, assuming that all colorectal cancers are derived from adenomatous polyps, may approach 40 per cent[21]. Advances in recombinant DNA technology may allow even more precise identification of those individuals at risk of harbouring an inherited predisposition to cancer, a concept first suggested by Warthin at the turn of the century[5].

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References

1. Office of Population Censuses and Surveys. *Mortality Statistics: Causes*. Series DH2, No. 15. London: HMSO, 1990.
2. Hardcastle JD, Thomas WM, Chamberlain J *et al.* Randomised, controlled trial of faecal occult blood screening for colorectal cancer. Results for the first 107 349 subjects. *Lancet* 1989; **i**: 1160–4.
3. Gyde S. Screening for colorectal cancer in ulcerative colitis: dubious benefits and high costs. *Gut* 1990; **31**: 1089–91.
4. Watkins DJG. A family tree. *Br Med J* 1904; **i**: 190.
5. Warthin AE. Heredity with reference to carcinoma as shown by the study of the cases examined in the pathological laboratory at the University of Michigan, 1895–1913. *Arch Intern Med* 1913; **12**: 546–55.
6. Woolf CM. A genetic study of carcinoma of the large intestine. *Am J Hum Genet* 1958; **10**: 42–7.
7. Houlston RS, Murday V, Harocopos C, Williams CB, Slack J. Screening and genetic counselling for relatives of patients with colorectal cancer in a family cancer clinic. *Br Med J* 1990; **301**: 366–8.
8. Lynch HT, Rozen P, Schuelke GS, Lynch JF. Hereditary colorectal cancer review: colonic polyposis and nonpolyposis colonic cancer (Lynch syndrome I and II). *Surg Dig Dis* 1984; **2**: 244–60.
9. Fitzgibbons RJ, Lynch HT, Stanislav GV *et al.* Recognition and treatment of patients with hereditary nonpolyposis colon cancer (Lynch syndromes I and II). *Ann Surg* 1987; **206**: 289–95.
10. Mecklin J-P. Frequency of hereditary colorectal carcinoma. *Gastroenterology* 1987; **93**: 1021–5.
11. Lynch HT, Fitzgibbons R, Marcus J *et al.* Colorectal cancer in a nuclear family. Familial or hereditary? *Dis Colon Rectum* 1985; **28**: 310–16.
12. Lovett E. Family studies in cancer of the colon and rectum. *Br J Surg* 1976; **63**: 13–18.
13. Maire P, Morichau-Beauchant M, Drucker J *et al.* Familiar prevalence of colorectal cancer; a 3-year case–control study. *Gastroenterol Clin Biol* 1984; **8**: 22–7.
14. Ponz de Leon M, Antoniolli A, Ascari A, Zanghieri G, Sacchetti C. Incidence and familial occurrence of colorectal cancer and polyps in a health-care district of northern Italy. *Cancer* 1987; **60**: 2848–59.
15. Bonelli L, Martines H, Conio M, Bruzzi P, Aste H. Family history of colorectal cancer as a risk factor for benign and

malignant tumours of the large bowel. A case control study. *Int J Cancer* 1988; **41**: 513–17.
16. Macklin MT. Inheritance of cancer of the stomach and large intestine in man. *J Natl Cancer Inst* 1960; **24**: 551–71.
17. Duncan JL, Kyle J. Family incidence of carcinoma of the colon and rectum in north-east Scotland. *Gut* 1982; **23**: 169–71.
18. Bishop DT, Burt RW. Genetic epidemiology and molecular genetics of colorectal adenomas and cancer. In: Rozen P, Reich CB, Winawer SJ, eds. *Large Bowel Cancer: Policy, Prevention, Research and Treatment. Frontiers of Gastrointestinal Research.* Basel: S. Karger, 1991; **18**: 99–114.
19. Gryska PV, Cohen AM. Screening asymptomatic patients at high risk for colon cancer with full colonoscopy. *Dis Colon Rectum* 1987; **30**: 18–20.
20. Rozen P, Fireman Z, Figer A, Legum C, Ron E, Lynch HT. Family history of colorectal cancer as a marker of potential malignancy within a screening program. *Cancer* 1987; **60**: 248–54.
21. Cannon-Albright LA, Skolnick MH, Bishop DT, Lee RG, Burt RW. Common inheritance of susceptibility to colonic adenomatous polyps and associated colorectal cancers. *N Engl J Med* 1988; **319**: 533–7.
22. Guillem JG, Neugut AI, Forde KA, Waye JD, Treat MR. Colonic neoplasms in asymptomatic first-degree relatives of colon cancer patients. *Am J Gastroenterol* 1988; **83**: 271–3.
23. Grossman S, Milos ML. Colonoscopic screening of persons with suspected risk factors for colon cancer. I. Family history. *Gastroenterology* 1988; **94**: 395–400.
24. Guillem JG, Forde KA, Treate MR, Neugut AI. The colonoscopic detection of adenomas in asymptomatic first-degree relatives of colon cancer patients: a controlled, prospective study. *Gastrointest Endosc* 1989; **35**: 172 (Abstract).
25. McConnell JC, Nizin JS, Slade MS. Colonoscopy in patients with a primary family history of colon cancer. *Dis Colon Rectum* 1990; **33**: 105–7.
26. McConnell JC. Colonoscopy or flexible proctosigmoidoscopy. *Dis Colon Rectum* 1990; **33**: 722.
27. Orrom WJ, Brzezinski WS, Wiens EW. Heredity and colorectal cancer: a prospective, community-based endoscopic study. *Dis Colon Rectum* 1990; **33**: 490–3.
28. Baker JW, Gathright JB, Timmcke AE, Hicks TC, Ferrari BT, Ray JE. Colonoscopic screening of asymptomatic patients with a family history of colon cancer. *Dis Colon Rectum* 1990; **33**: 926–30.
29. Herrera L, Hanna S, Petrelli N, Nava H. Screening endoscopy in patients with family history positive (FH+) for colorectal neoplasia (CRN). *Gastrointest Endosc* 1990; **36**: 211 (Abstract).
30. Stephenson BM, Finan PJ. Colonoscopy or flexible proctosigmoidoscopy. *Dis Colon Rectum* 1990; **33**: 722.
31. Stephenson BM, Finan PJ, Bishop DT. Colonoscopic screening. *Dis Colon Rectum* 1990; **33**: 1075–6.
32. Jass JR. Do all colorectal carcinomas arise in preexisting adenomas? *World J Surg* 1989; **13**: 45–51.
33. Fujita M, Sugiyama R, Kumanishi Y *et al.* Evaluation of effectiveness of mass screening for colorectal cancer. *World J Surg* 1990; **14**: 648–53.
34. Eddy DM, Nugent FW, Eddy JF *et al.* Screening for colorectal cancer in a high-risk population. *Gastroenterology* 1987; **92**: 682–92.

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Reversal of Hartmann's procedure: timing and operative technique

A review of closure of Hartmann's colostomy was undertaken to establish guidelines for the timing and technique of reversal. Between 1984 and 1990 there were 69 reversals; 48 patients originally had diverticular disease and 21 had carcinoma. One-third underwent reversal before 4 months and two-thirds after this time. The operative mortality rate was 3 per cent and the anastomotic leak rate 4 per cent. Significant morbidity occurred in 30 per cent. There was no advantage in delayed closure. Complications occurred in 24 per cent of patients undergoing reversal before and 35 per cent undergoing reversal after 4 months. Thirty-five anastomoses were hand-sewn and 34 stapled. There were no differences in operating time for the two techniques, but a greater number were stapled after 4 months than before ($P < 0.05$), which may reflect increased rectal stump shrinkage with time. There were no differences in complication rates whether the anastomosis was hand-sewn (34 per cent) or stapled (26 per cent). Closure of Hartmann's colostomy is a safe procedure but has a significant morbidity in nearly one-third of cases. On the basis of these results, there is no indication to delay closure after 4 months have elapsed, and earlier reversal, when the rectal stump is most accessible, is recommended.

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When Henri Hartmann described the operation which now bears his name in 1921[1] it was carried out for carcinoma of the pelvic colon. More recently, Boyden[2] popularized the technique for complicated diverticular disease for which it has now become a standard procedure. By 1984 Krukowski and Matheson[3], in a review of the literature, were able to report an operative mortality rate of 12·2 per cent for cases of complicated diverticular disease with peritonitis. This compared favourably with techniques of drainage and defunction, with the affected segment left *in situ*, where the mortality rate was higher.

Despite the advent of on-table colonic lavage and primary anastomosis for obstructing left-sided colonic lesions[4,5], and a recent report of favourable results of primary anastomosis without on-table bowel preparation[6], Hartmann's procedure is still frequently carried out for carcinoma when the fitness of the patient may demand a simpler operation, when the surgeon is less experienced in primary reconstructive techniques or when there is extensive pelvic involvement with tumour.

Hartmann had not originally envisaged reversal of the procedure but this is now usually the aim of the surgeon where circumstances permit. In patients who survive the initial operation, many with carcinoma will not undergo reversal because of recurrent or metastatic disease. After resection for diverticular disease, about two-thirds of those available eventually have their colostomy closed[7].

Whilst the complications of Hartmann's procedure have been extensively documented, less attention has been paid to the reversal operation. There are no objective guidelines for the timing and technique of this operation and most studies analysing the complications of reversal of Hartmann's colostomy group it with closures of loop colostomies, which seems inappropriate.

The reversal procedure may pose technical problems and various manoeuvres to facilitate the operation are reported. These include sigmoidoscopic identification of the rectal stump[8], suspension of the rectal stump from the pelvic brim[9], use of long sutures to identify the rectal stump[10], limited distal resection with formation of a mucus fistula[11], side-to-end colorectal anastomosis[12] and use of detachable-head stapling devices[13,14]. *Table 1* reviews the reported morbidity and mortality of closure of Hartmann's colostomy, with an overall mortality rate of 2·3 per cent and anastomotic leak rate of 10 per cent. There is less information on techniques of anastomosis, but *Table 2* describes the reported results comparing stapled and hand-sewn anastomoses. With regard to timing of reversal, Pearce and Karran[22] found a high complication rate with early closure. Fistulae occurred in six of 12 patients whose colostomy was closed before 3 months and seven of 28

Table 1 *Mortality and anastomotic leak rates following closure of Hartmann's colostomy*

Author	No. of cases	Leak rate (%)	Deaths (%)
Bell *et al.*[11] 1980	70	9	3
Bakker *et al.*[15] 1982	12	0	0
Ling and Adberg[16] 1984	18	6	6
Hackford *et al.*[17] 1985	10	0	0
Foster *et al.*[18] 1985	54	15	?
Pittman and Smith[19] 1985	37	11	0
Shepherd and Keighley[20] 1986	12	12	8
Tudor and Keighley[21] 1987	25	4	0
Pearce and Karran[22] 1989	80	16	4
Whiston *et al.*[23] 1989	40	2·5	0
Cumulative total	358	10%	2·3%

Table 2 *Comparison between hand-sewn and stapled techniques of anastomosis in reversal of Hartmann's procedure*

		Leak rate	
Author	No.	Hand-sewn	Stapled
Pittman and Smith[19]	37	No difference	
Foster *et al.*[18]	54	7 of 44 (16%) *versus* 1 of 10 (10%)	
Whiston *et al.*[23]	40	1 of 29 (3%) *versus* 0 of 11 (0%)	
Pearce and Karran[22]	80	No difference	

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Table 3 *Time interval from Hartmann's procedure to colostomy closure after operation for diverticular disease and carcinoma*

	Time interval (months)					
	<2	2–3	3–4	4–6	6–12	>12
Diverticular disease	2	6	8	18	10	4
Carcinoma	2	4	3	4	5	3
Total no. of cases	4	10	11	22	15	7

undergoing reversal between 3 and 6 months. Pittman and Smith[19] found more complications in those patients undergoing reversal before 4 weeks who initially had had intraperitoneal perforation and in those undergoing reversal within 8 weeks if they had had initial colostomy complications.

We recently reported that the Hartmann's rectal stump undergoes involution after defunction and that by 3 months the rectal stump volume has decreased by 35 per cent of its original volume[24]. These changes are associated with changes of diversion colitis in the rectal mucosa. This is seen in all cases by 3 months and is characterized by chronic inflammation with lymphoid hyperplasia in the absence of crypt distortion or crypt abscesses[25]. By 6 months these changes have progressed further and may increase the difficulty of the reversal procedure.

The aims of this study were to analyse critically closure of Hartmann's colostomy by comparing the complications of surgery with the time interval from formation to reversal and with the technique of anastomosis.

Patients and methods

The hospital records of patients who underwent reversal of Hartmann's procedure in Derriford and Freedom Fields Hospitals, Plymouth between 1984 and 1990 were reviewed. A detailed analysis was made of those who presented originally with septic complications of diverticular disease and complicated rectosigmoid and sigmoid carcinoma. Closure of Hartmann's colostomy created for other conditions was excluded to focus on the two most common conditions for which this procedure is performed. The cases excluded were those operated on for trauma, colonoscopic perforation, volvulus, haemorrhage and cases where a mucus fistula was fashioned rather than an oversewn rectal stump.

Sixty-nine patients were identified: 48 had diverticular disease, 25 women, median age 67 (range 41–84) years and 23 men, median age 66 (45–82) years; and 21 with carcinoma, 13 women, median age 66 (59–86) years and eight men, median age 76 (57–83) years. During this period, 107 Hartmann procedures were performed which were not reversed in the Plymouth hospitals. These were performed for various conditions as well as diverticular disease and carcinoma. With the 69 study patients and 11 patients with other pathologies, this represents a crude colostomy closure rate of 43 per cent. The main reasons for not closing the colostomy in patients with carcinoma were death and metastatic disease. After operations for diverticular disease the reasons were death, cardiorespiratory disease and the patient's wishes.

The following criteria were analysed: pathology at the original operation, time interval to reversal, grade of operating surgeon, anastomotic technique, operating time, complications of colostomy closure, and length of hospital stay. A comparison was made between cases of diverticular disease and carcinoma, and the techniques and timing of closure were compared in relation to operating time and complications.

Results

Pathology

An analysis of operative findings and histopathology reports demonstrated that of the 48 patients with diverticular disease, 18 presented with a phlegmon or mass, 12 with peridiverticular abscess, 12 with purulent peritonitis with or without a mass and four with faecal peritonitis with or without a mass. The resected segment of bowel was a median 15 (range 7–42) cm in length.

Two patients presented with complicated sigmoid diverticular disease but had associated carcinoma, one with faecal peritonitis and a Dukes' C lesion and one with a diverticular abscess and a Dukes' C lesion.

Of the 21 patients with carcinoma, 14 presented with large bowel obstruction, five with a mass and two with perforation. There were no Dukes' A cases, 17 Dukes' B and four Dukes' C. The resected bowel measured a median of 18 (range 9–30) cm.

Time interval to colostomy closure

Table 3 shows the time interval from Hartmann's procedure to reversal. For diverticular disease, the median was 4·5 months (range 6 weeks to 2 years 9 months), and for carcinoma the median was 4·5 months (range 5 weeks to 3 years). Overall, 36 per cent of colostomies were closed before 4 months and 64 per cent at 4 months or later. Four months was arbitrarily taken to compare early and late reversal. These groups were comparable with respect to sex ratio: 11 men and 14 women underwent reversal before 4 months, and 20 men and 24 women had reversal after 4 months. Similarly, there were no differences in the severity of sepsis in patients with diverticular disease, whether undergoing reversal early or late. Purulent or faecal peritonitis was found in six of 15 cases in which the colostomy was closed before 4 months and in 11 of 31 closed after 4 months.

Surgeon and operating time

The original Hartmann's procedure was carried out by a consultant or with a consultant surgeon present in 22 (32 per cent) cases and by a senior registrar or registrar in 47 (68 per cent); these were all emergency or urgent operations. By contrast, the majority (54: 78 per cent) of reversal operations were by a consultant surgeon and 15 (22 per cent) by a trainee.

The length of operation for closure of the colostomy was taken as the anaesthetic time from entering to leaving theatre. For consultant operations the median time was 2 h 20 min (range 55 min to 4 h 15 min) and for registrars, 3 h (range 1 h 45 min to 4 h 45 min).

Anastomotic technique

The reversal operations involved eight consultant surgeons and seven registrars. The technique used was decided by the individual surgeon. Where stapled anastomoses were undertaken, these were almost invariably using the Premium CEEA® (US Surgical Corporation, Norwalk, Connecticut, USA) using the technique of introducing the spike through the closed rectal stump. A variety of techniques and materials were used for hand-sewn anastomosis with interrupted one-layer or continuous two-layer sutures.

Overall, 35 anastomoses were hand-sewn and 34 stapled. In patients with diverticular disease, 22 were hand-sewn and 26 stapled, and in patients with carcinoma 13 were hand-sewn and eight stapled. Of the stapled anastomoses where the size of the stapling device was documented ($n = 28$) there were 14 of 31 mm, eight of 28 mm and six of 25 mm.

There were no differences in the time taken with the two techniques. For hand-sewn reversal the median time was 2 h 30 min (range 1 h to 4 h 45 min), and for stapled reversal the median time was 2 h 45 min (range 1 h 15 min to 4 h 30 min).

However, there were differences in the time interval to colostomy closure with the two anastomotic techniques. For those reversals carried out within 4 months, nine were stapled and 14 hand-sewn, whilst after 4 months stapling was more frequent, with 28 cases as opposed to 18 hand-sewn ($P < 0.05$, χ^2 test).

Morbidity and mortality of colostomy closure

The complications of Hartmann's reversal are outlined in *Table 4*. There were two deaths, an operative mortality rate of 3 per cent. Significant morbidity occurred in 21 patients (30 per cent).

Table 4 *Complications of closure of colostomy after Hartmann's procedure related to anastomotic technique and time interval from the primary operation*

Patient no.	Complication	Technique	Time (months)
1	Anastomotic deshiscence, peritonitis, death	Hand-sewn	8·5
2	Acute renal failure, death	Stapled	15
3	Enterocutaneous fistula	Hand-sewn	6·25
4	Rectovesical and rectovaginal fistula	Hand-sewn	3·5
5–8	Small bowel obstruction	2 Stapled	4, 4
		2 Hand-sewn	2, 4·5
9–14	Wound infection	2 Stapled	7, 7
		4 Hand-sewn	2, 16, 1·25, 3
15–19	Incisional hernia	2 Stapled	4, 11
		3 Hand-sewn	11, 1·5, 5·25
20	Wound infection and incisional hernia	Stapled	15
21	Pulmonary embolism	Stapled	4·25

One patient died from peritonitis following anastomotic dehiscence, another developed an enterocutaneous fistula from an assumed anastomotic leak and one patient developed rectovesical and rectovaginal fistulae; this represents a clinical anastomotic leak rate of 4 per cent. The other patient who died developed acute renal failure and died 3 days after operation. Small bowel obstruction requiring laparotomy occurred in four patients (6 per cent), significant wound infection in seven (10 per cent), and incisional hernia in six (9 per cent).

Intraoperative problems were encountered with stapled anastomosis in five cases. Two cases had defects in the anastomosis requiring conversion to hand-sewn anastomosis, one of which was defunctioned with a transverse colostomy. In one case the anastomosis separated as the gun was withdrawn and the stapled anastomosis was repeated. In one patient the rectal stump required dilatation to admit the gun and in one case the gun was passed inadvertently into the mesorectum. This mishap was not recognized until after firing the staples, and it was necessary to convert to a hand-sewn anastomosis. All these complications occurred in cases closed more than 4 months from the original operation.

There was no difference in the incidence of major complications between the two techniques of anastomosis. However, all three anastomotic leaks or fistulae occurred in hand-sewn anastomoses. Similarly, there was no reduction in complications with delayed re-anastomosis. Of 25 colostomy closures carried out before 4 months, six (24 per cent) had complications, and of 43 closed at 4 months or later, 15 (35 per cent) had complications. There was no difference in the complication rate when the operation was for diverticular disease or carcinoma. There was also no difference in the complication rate when the original operation was an emergency (52 cases) or urgent (17 cases). The grade of surgeon did not influence the complication rate. All three anastomotic leaks or fistulae occurred after operations performed by a consultant surgeon, and general complications occurred in 32 per cent of consultant cases and 25 per cent of trainees' cases.

The length of hospital stay was similar for patients with diverticular disease and carcinoma; median 13 days (range 9–35 days) and 15 days (range 11–36 days), respectively. On follow-up so far, at a median of 4 years, there have been no clinically apparent anastomotic strictures.

Discussion

The results suggest that re-anastomosis after Hartmann's procedure is a safe operation in terms of operative mortality and anastomotic leak rates. This series, with an operative mortality rate of 3 per cent and a leak rate of 4 per cent, compares favourably with other reported series. The operation does, however, carry significant morbidity in nearly one-third of cases, requires an experienced surgeon to perform the procedure, takes up the majority of one operating session and will keep the patient in a hospital bed for 2 weeks.[4] When performed for carcinoma, it seems that few patients with perforation or Dukes' C lesions at the initial operation will have the colostomy closed but those that undergo re-anastomosis show no difference in morbidity when compared with cases of diverticular disease.

Stapled anastomoses were more frequently performed than hand-sewn anastomoses, with a longer time interval between resection and re-anastomosis. This may reflect the rectal stump shrinkage that occurs with time, re-anastomosis in the small shrunken rectal stump being easier by the stapled technique. Physiological studies have demonstrated that rectal stump volume decreases with time after defunction[24] and it was also clinically apparent at the time of reversal that the length of the rectal stump had decreased and the stump had disappeared into the pelvis in many patients with a delayed closure. There was no difference between the two anastomotic techniques in operating time, possibly because the anastomosis takes up a small part of the overall time in theatre, or possibly because stapled anastomosis was more frequently undertaken in the more difficult cases with dense adhesions and an inaccessible rectal stump. There were no differences in the complication rates between the two techniques. However, it should be noted that all three anastomotic leaks or fistulae occurred in hand-sewn anastomoses. The few intraoperative problems encountered with stapling devices are not exceptional but, surprisingly, no clinically significant anastomotic strictures have so far been detected.

In contrast to other authors[14,22], we found no increased morbidity with colostomy closure before 4 months or even before 3 months and, on the basis of these results, we recommend earlier re-anastomosis when the rectal stump is more accessible.

Of the methods reported to facilitate subsequent re-anastomosis after Hartmann's procedure, formation of a distal mucus fistula seems an attractive approach. However, when performed for carcinoma, this may compromise the cancer resection and in diverticular disease with a large phlegmon it is often not practical as resection needs to be carried to the pelvic brim. If a limited resection is performed in diverticular disease, the remaining affected segment should be adequately excised with mobilization of the splenic flexure at the operation to close the colostomy, as recurrence of complications can occur in 12·5 per cent of cases when limited resection is performed[26].

Given that colostomy closure may not be performed in one-half of cases, and that the re-anastomosis carries a significant morbidity, there is a strong case for considering primary resection and anastomosis at the initial operation. Favourable results have been reported with this approach[27] but patient selection is crucial. Hartmann's procedure can be a life-saving procedure in the severely ill patient when there is peritonitis. It is not known whether a longer procedure with on-table lavage and primary anastomosis would lead to increased mortality in complicated cases. This would only be answered by a prospective trial comparing Hartmann's procedure with primary anastomosis in the emergency situation. For the present, Hartmann's procedure remains a useful part of the surgeon's repertoire. This study has shown that the colostomy may subsequently be closed within 4 months without excessive morbidity.

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References

1. Hartmann H. Nouveau procède d'ablation des cancers de la partie terminale du colon pelvien. *Trentième Congrès de Chirurgie* (Strasbourg, France, 1921) 41.

2. Boyden AM. The surgical treatment of diverticulitis of the colon. *Ann Surg* 1950; **132**: 94–109.
3. Krukowski ZH, Matheson NA. Emergency surgery for diverticular disease complicated by generalised and faecal peritonitis: a review. *Br J Surg* 1984; **71**: 921–7.
4. Dudley HAF, Radcliffe AG, McGeehan D. Intraoperative irrigation of the colon to permit primary anastomosis. *Br J Surg* 1980; **67**: 80–1.
5. Thomson WHF, Carter SStC. On-table lavage to achieve safe restorative rectal and emergency left colonic resection without covering colostomy. *Br J Surg* 1986; **72**: 61–3.
6. Dorudi S, Wilson NM, Heddle RM. Primary restorative colectomy in malignant left-sided large bowel obstruction. *Ann R Coll Surg Engl* 1990; **72**: 393–5.
7. Haas PA, Haas GP. A critical evaluation of the Hartmann's procedure. *Am Surg* 1988; **54**: 380–5.
8. Gervin AS, Fischer RP. Identification of the rectal pouch of Hartmann. *Surg Gynecol Obstet* 1987; **164**: 176–8.
9. Rushden RO, Kusminsky R. Closure of Hartmann's procedure. *Am Surg* 1982; **48**: 528.
10. Madura JA, Fiore AC. Re-anastomosis of a Hartmann rectal pouch. *Am J Surg* 1983; **145**: 279.
11. Bell GA, Parton ONM. Hartmann resection for perforated sigmoid diverticulitis. *Dis Colon Rectum* 1984; **27**: 253–6.
12. Bell GA. Closure of colostomy following sigmoid colon resection for perforated diverticulitis. *Surg Gynecol Obstet* 1980; **150**: 85–90.
13. Ramirez OM, Hernandez-Pombo J, Marupudi SR. New technique for anastomosis of the intestine after the Hartmann's procedure with end-to-end anastomosis stapler. *Surg Gynecol Obstet* 1983; **156**: 367–8.
14. Sloun MS, Krebs HB, Wheelock JB. A simplified technique for intestinal re-anastomosis after the Hartmann procedure. *Surg Gynecol Obstet* 1985; **161**: 390–1.
15. Bakker FC, Hoitsma HFW, Den Otter G. The Hartmann procedure. *Br J Surg* 1982; **69**: 580–2.
16. Ling L, Adberg S. Hartmann procedure. *Acta Chir Scand* 1984; **150**: 413–17.
17. Hackford AW, Schoetz DJ Jr, Coller JA *et al.* Surgical management of complicated diverticulitis, the Lahey Clinic experience, 1967 to 1982. *Dis Colon Rectum* 1985; **28**: 317–21.
18. Foster ME, Leaper DJ, Williamson RCN. Changing patterns in colostomy closure: the Bristol experience 1975–1982. *Br J Surg* 1985; **72**: 142–5.
19. Pittman DM, Smith LE. Complications of colostomy closure. *Dis Colon Rectun* 1985; **28**: 836–43.
20. Shepherd AA, Keighley MRB. Audit on complicated diverticular disease. *Ann R Coll Surg Engl* 1986; **68**: 8–10.
21. Tudor RG, Keighley MRB. The options in surgical treatment of diverticular disease. *Surg Annu* 1987; **19**: 135–49.
22. Pearce N, Karan SJ. Hartmann's reversal—when and how? *Gut* 1989; **30**: 1470 (Abstract).
23. Whiston R, Armitage NC, Hardcastle JD. *An Appraisal of Hartmann's Procedure.* Edinburgh: Association of Surgeons of Great Britain and Ireland, 1989.
24. Roe AM, Brown C, Brodribb AJM. Changes in the defunctioned anorectum following Hartmann's operation. *Br J Surg* 1990; **70**: 1426.
25. Roe AM, Warren BF, Brodribb AJM *et al.* Diversion colitis and involution of the defunctioned anorectum. *Gut* 1990; **32**: 1174 (Abstract).
26. Benn PL, Wolf BG, Ilstrup DM. Level of anastomosis and recurrent colonic diverticulitis. *Am J Surg* 1986; **151**: 269–71.
27. Peoples JB, Vilk DR, Maguire JP *et al.* Reassessment of primary resection of the perforated segment for severe colonic diverticulitis. *Am J Surg* 1990; **159**: 291–3.

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Risk of strangulation in groin hernias

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Although the elective repair of groin hernias is advised to prevent strangulation, the likelihood of this complication occurring is unknown. To quantify this risk, the cumulative probability of strangulation in relation to the length of history has been calculated for inguinal and femoral hernias presenting to this hospital between 1987 and 1989. Of 476 hernias (439 inguinal, 37 femoral), there were 34 strangulations (22 inguinal, 12 femoral). After 3 months the cumulative probability of strangulation for inguinal hernias was 2·8 per cent, rising to 4·5 per cent after 2 years. For femoral hernias the cumulative probability of strangulation was 22 per cent at 3 months and 45 per cent at 21 months. The rate at which the cumulative probability of strangulation increased was in both cases greatest in the first 3 months, suggesting that patients with a short history of herniation should be referred urgently to hospital and given priority on the waiting list.

Strangulated external hernias account for about 25 per cent of cases of intestinal obstruction[1] and are associated with significant rates of mortality and morbidity[2], particularly in the elderly[3]. Although the elective repair of groin hernias is advised, the urgency with which operation should be undertaken to minimize the risk of strangulation is uncertain. The aim of this study was to determine how the risk of strangulation in femoral and inguinal hernias varies in relation to their duration.

The ideal population group from which to derive this information would be one for which no elective surgery was available and the incidence and prevalence of hernia was known, and for which hernia repair occurred only at strangulation. Although a study approaching this ideal has been carried out in Cali, Columbia, no attempt was made to relate the risk of strangulation to variations in the length of history[4]. In Britain no such comparable study group exists. To estimate the risk of strangulation we have relied on a hospital based population, i.e. patients referred both for elective and for emergency hernia repair.

Patients and methods

A list of all adult patients (age ≥ 14 years) undergoing repair of inguinal or femoral hernias at University College Hospital, London from 1987 to 1989 inclusive was obtained from the operating registers. The notes of these patients were examined, and details of age, sex, type of hernia and its duration recorded. Strangulation was assessed in two different ways; firstly, as a working diagnosis that led to an immediate operation and, secondly, as the finding at operation of tissue whose viability was already compromised.

To calculate the cumulative probability of strangulation for each of the time intervals at which it was recorded, the Kaplan–Meier estimate[5] was used. This estimate is usually employed to describe the survival experience of a group of patients when knowledge of the survival times is incomplete; all that is known about the survival of these patients is that they have not yet died. This situation is analogous to using the Kaplan–Meier technique to estimate the probability of strangulation as a function of the length of history; the observation of the hernia when it is repaired electively is necessarily incomplete in the sense that all that can be said is that strangulation had not occurred up to the time of operation. The cumulative probabilities of strangulation at various times are given with the 95 per cent confidence intervals (CI)[6].

Results

In the 3 years studied, 561 hernias were repaired, of which adequate records were available on 476 (84·8 per cent). There were 439 inguinal hernias and 37 femoral hernias, an inguinal:femoral hernia ratio of approximately 12:1. Of the patients undergoing elective repair, 38 per cent came from outside our district as did 26 per cent presenting with strangulation. No patient developed strangulation while on the waiting list and there were no hospital deaths after either elective or emergency operation.

Inguinal hernia

Twenty-two (5·0 per cent) of the 439 inguinal hernias presented as emergencies with a working diagnosis of strangulation. Of these 22 patients, 14 (64 per cent) had evidence of compromised tissue at operation. However, in only one case was it necessary to resect a strangulated loop of bowel. Four of the strangulations occurred in recurrent hernias, of which there were a total of 60. The median age of patients presenting with a clinically strangulated inguinal hernia was 65·5 years (range 17–87 years) and for those with non-strangulated hernias it was 59 years (range 19–89 years). A plot of the cumulative probability of an inguinal hernia presenting as clinically strangulated *versus* length of history is shown in *Figure 1*. The cumulative probability of strangulation at 3 months was 2·8 per cent (95 per cent CI, 1·1–4·5 per cent), at 24 months 4·5 per cent (95 per cent CI, 1·3–7·7 per cent) and at 60 months 8·6 per cent (95 per cent CI, 2·6–14·6 per cent). In other words, approximately one-third of the cumulative risk of strangulation at 60 months was reached in the first 3 months of a hernia's presence.

Femoral hernia

Of the 37 femoral hernias, 12 (32 per cent) presented with a working diagnosis of strangulation. Of these 12, 11 (92 per cent) had evidence of strangulated tissue at operation. Five patients required resection of strangulated bowel. A plot of the cumulative probability of a femoral hernia presenting as clinically strangulated *versus* length of history is shown in *Figure 2*. At 1 month, the cumulative probability of strangulation was 22 per cent (95 per cent CI, 8·3–35·7 per cent) and at 21 months 45 per cent (95 per cent CI, 23–67 per cent). The greatest proportion (about 50 per cent in this case) of the accumulated risk of a femoral hernia strangulating at 21 months was therefore seen within 1 month of its appearance.

Summary of results

The evidence presented indicates that, although the cumulative probability of strangulation increases with time, the rate at

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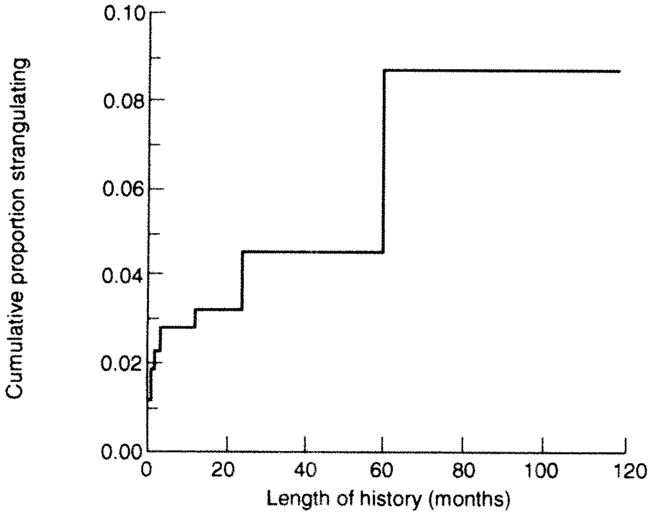
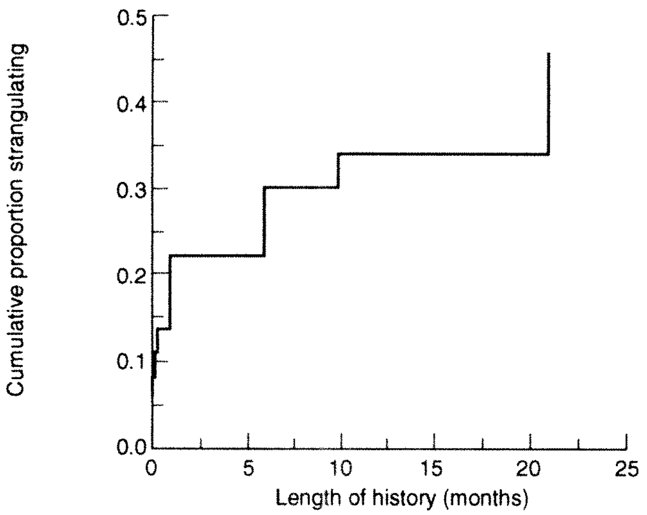


Time (months)	0.03	0.5	1.0	1.2	2.0	3.0	12.0	24.0	60.0
Patients at risk	439	433	431	411	401	369	237	151	70
Strangulations	4	1	2	1	2	2	1	2	3

Figure 1 *Plot of the cumulative proportion of inguinal hernias strangulating* versus *length of history. Approximately one-third of the total cumulative risk of strangulation seen at 60 months occurs within the first 3 months of their presence. (The three strangulations which took place at 120 months and the one strangulation at 240 months are not shown)*



Time (months)	0.03	0.06	0.16	0.25	1.0	6.0	10.0	21.0
Patients at risk	37	35	34	33	30	20	18	9
Strangulations	2	1	1	1	3	2	1	1

Figure 2 *Plot of the cumulative proportion of femoral hernias strangulating* versus *length of history. Approximately one-half of the total cumulative risk of strangulation seen at 21 months occurs within the first month*

which it is accumulating is never greater than during the first 3 months after recognition of the hernia. This conclusion applies to both inguinal and femoral hernias.

Discussion

Information on the likelihood of strangulation in groin hernias is scarce. One study, quoted by Neuhauser[4], suggests that the probability of strangulation per inguinal hernia year is 0·00291. However, calculations based on this figure must assume that the risk of strangulation remains constant for each year of a hernia's presence. Although there is support for this view[7], the observations of others contradict it; strangulation was seen as either the first sign of herniation or occurring shortly (< 7 days) thereafter in between 11 and 24 per cent of inguinal hernias and between 16 and 62 per cent of femoral hernias[8,9]. The present results confirm and quantify these observations by showing that the rate of change in the cumulative probability of strangulation is not constant, but increases rapidly over the first 3 months of the existence of a hernia.

Bias may occur from using a teaching hospital population to estimate the risk of strangulation. It is conceivable that the number of strangulations has been under-reported, with patients from other districts on our waiting list more likely to attend their district hospital in the event of an emergency. Against this, however, are our incidences of strangulation which, for both inguinal (5·0 per cent) and femoral hernias (32 per cent), were similar to those of a much larger series[8]. Also, reasonably comparable percentages of patients presented from outside the district both for elective (38 per cent) and emergency surgery (26 per cent).

The Kaplan–Meier estimate, as used here, relies on the ratio of strangulated to non-strangulated hernias present at particular lengths of history. Any policy which alters either the numerator or the denominator of this ratio will alter the estimated risk of strangulation. Because of the relatively small number of patients involved in this study, we have not attempted to identify subgroups at greater risk of strangulation, e.g. those presenting with recurrent or painful herniation, in whom earlier operation might be offered. We recognize that a policy of 'preferential surgery', by reducing the number of hernias available for study at longer time intervals, i.e. the denominator, will lead to an over-estimate of the risk of strangulation for hernias of longer duration. Similarly, the length of the waiting list could also affect the calculation of risk. However, there is evidence to suggest that even in the absence of a waiting list the rate of emergency operations for inguinal hernias remains unaltered[10]. In the present study none of the patients who presented with strangulation was on the waiting list (median waiting time 5 months, range 0·25–40 months) and hence the numerator was unaffected by this variable. The absence of patients strangulating while on the waiting list is partially explained by the difference in the lengths of history between those patients who presented as emergencies (median 2·5 months, range 0·03–240 months) and those receiving elective surgery (median 16 months, range 0·25–720 months). It would appear that hernias which strangulate do so before referral to hospital. It is also possible that the number of patients on the waiting list in this study was too small to observe the expected number of strangulations, given the probability of this event occurring. Thus for the 417 inguinal hernias repaired electively (median length of history 16 months), the estimated cumulative risk of strangulation occurring during the median waiting list period of 5 months would be between 0·13 per cent and 1·1 per cent, i.e. between 0·5 (or effectively none) and 4·5 patients would be expected to strangulate.

The probabilities calculated in this study may be used to estimate the likelihood of strangulation occurring before a patient on the waiting list is admitted. *Table 1* presents these probabilities for patients placed on a 1-month or 1-year waiting list with inguinal hernias which have been present for either 1 or 12 months; the associated risk of death from the strangulated hernia is also shown. We have considered the mortality rate from strangulated inguinal hernia to be in the order of 13 per cent[2], but we accept that this is a general figure which takes no account of the effect of age or the need for bowel resection.

Although a long waiting list increases the risk of strangulation and death, the magnitude of the increase depends on the length of history of the hernia at the time of presentation. For inguinal hernias with a short history, the danger of delay is greater than for hernias of longer duration.

This study suggests that there may be a case for giving patients with a short history of herniation priority on the

Table 1 *Probabilities of death and strangulation for inguinal hernias according to length of history and waiting list time*

Length of history (months)	Waiting list time (months)	Probability of strangulation before operation (%)	Probability of death from strangulation (%)
1	1	0·7	0·09
	12	1·6	0·2
12	1	0·1	0·013
	12	1·3	0·17

The mortality rate associated with strangulation has been taken as 13 per cent[2]

waiting list. This assumes of course that the patients are on the waiting list in the first place. The real problem in reducing the incidence of strangulation appears to lie with the referral of those patients most at risk to hospital. At present the emergency population would seem to be separate from the waiting list population[10]. The public, and especially the elderly, should therefore be warned of the potential dangers of a lump in the groin, and general practitioners should be encouraged to refer such patients promptly, i.e. during the first 3 months of the existence of the hernia.

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References

1. McEntee G, Pender D, Mulvin D *et al.* Current spectrum of intestinal obstruction. *Br J Surg* 1987; **74**: 976–80.
2. Andrews NJ. Presentation and outcome of strangulated external hernia in a district general hospital. *Br J Surg* 1981; **68**: 329–32.
3. Tingwald GR, Cooperman M. Inguinal and femoral hernia repair in geriatric patients. *Surg Gynecol Obstet* 1982; **154**: 704–6.
4. Neuhauser D. Elective inguinal herniorrhaphy versus truss in the elderly. In: Bunker JP, Barnes BA, Mosteller F, eds. *Costs, Risks and Benefits of Surgery*. New York: Oxford University Press, 1977: 223–39.
5. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. *J Am Stat Ass* 1958; **49**: 457–81.
6. Machin D, Gardner MJ. Calculating confidence intervals for survival time analyses. In: Gardner MJ, Altman DG, eds. *Statistics with Confidence*. London: British Medical Journal, 1989: 64–70.
7. Beller AJ, Colp R. Strangulated hernia from the standpoint of the viability of the intestinal contents. *Arch Surg* 1926; **12**: 901–18.
8. Frankau C. Strangulated hernia: a review of 1487 cases. *Br J Surg* 1931; **19**: 176–91.
9. McEntee GP, O'Carroll A, Mooney B, Egan TJ, Delaney PV. Timing of strangulation in adult hernias. *Br J Surg* 1989; **76**: 725–6.
10. Quill DS, Devlin HB, Plant JA, Denham KR, McNay RA, Morris D. Surgical operation rates: a twelve year experience in Stockton on Tees. *Ann R Coll Surg Engl* 1983; **65**: 248–53.

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Identification of bile duct stones in patients undergoing laparoscopic cholecystectomy

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To identify patients with common bile duct stones, all patients considered for laparoscopic cholecystectomy in this unit undergo intravenous cholangiography (IVC) with tomography and, more recently, operative cholangiography. To date 100 consecutive patients with symptomatic gallstones have undergone laparoscopic cholecystectomy with no specific exclusion criteria. Eight patients of 100 were found to have duct stones on IVC with one false-positive. These IVC data were compared with data from 52 patients who also had operative cholangiograms performed. One stone was detected on operative cholangiography that was not identified on IVC. No additional information was gained from operative cholangiography. These data suggest that preoperative IVC is adequate for the detection of duct stones in patients considered for laparoscopic cholecystectomy.

With the rapid and widespread acceptance of laparoscopic cholecystectomy as the preferred primary operation for cholelithiasis[1–4], the identification of common duct stones becomes clinically important. Ideally, such stones should be identified before cholecystectomy and removed by endoscopic retrograde cholangiopancreatography (ERCP) if possible. If this procedure is unsuccessful then open cholecystectomy and duct exploration may be necessary.

Evidence from open cholecystectomy suggests that 2–12 per cent of patients with no evidence to suggest duct stones will have such stones demonstrated on operative cholangiography[5,6]. Intravenous cholangiography (IVC) has been generally regarded as diagnostically inferior to operative cholangiography. Hence, in some centres operative cholangiography has become an integral part of laparoscopic cholecystectomy. This manoeuvre may increase the difficulty and duration of the laparoscopic procedure and in its own right is not of course completely accurate. This study was undertaken to assess the value of IVC in identifying ductal stones before operation and to compare it with operative cholangiography. If IVC proved diagnostically similar to operative cholangiography, then the latter could be dispensed with or used only in selected cases.

Patients and methods

From July 1990 to March 1991 at one institution 100 consecutive patients with symptomatic gallstones underwent laparoscopic cholecystectomy with no conversion to open cholecystectomy. All operations were performed using a standard laparoscopic technique[2]. Ages ranged from 17 to 83 years (mean 49 years); there were 68 women and 32 men. All patients were classified before operation by the ASA grading system[7]. Ninety-eight patients were ASA grade I–II, and two patients were ASA grade III. All patients had biliary tract ultrasonographic examination and/or oral cholecystography before surgery to establish the diagnosis. In addition, all patients had baseline liver biochemistry measurements and all had IVC performed on the day before, or on the morning of, surgery. IVC was performed using a drip infusion of Biliscopin (Schering AG, Berlin, Germany). The contrast meglumine iotroxate (100 ml, 50 mg/ml) was infused over a period of 30 min. Tomography was also used to improve the clarity of the images. If duct stones were detected by IVC then patients underwent ERCP, sphincterotomy and stone extraction, if required, before laparoscopic cholecystectomy. As expertise in the technique of laparoscopic cholecystectomy was being developed, the first 40 patients did not have operative cholangiography. The remaining 60 patients all had operative cholangiography attempted.

Results

Indications for cholecystectomy are summarized in *Table 1*. Two patients developed a mild reaction from the injection of contrast; this did not require any treatment. Nine patients were deemed to have duct stones on IVC. This was confirmed by ERCP in eight cases with one false-positive. All eight patients underwent sphincterotomy and stone extraction before laparoscopic cholecystectomy. Ultrasonography of the common bile duct was unreliable in the detection of stones when compared with IVC or ERCP. Only one common duct stone was demonstrated by ultrasonography. Bile duct dilatation was demonstrated by preoperative ultrasonography in one of nine patients with common duct stones and in six of 76 patients without duct stones.

Sixty patients had operative cholangiography attempted. This was successful in 52 patients, with eight failures (13 per cent failure rate). All failures occurred in the first 30 attempts. The IVC data on these 52 patients undergoing successful operative cholangiography were compared with the operative cholangiographic data. Only one patient was found to have a small common bile duct stone on operative cholangiography that was not identified on IVC. All patients found to have duct stones by IVC or operative cholangiography had abnormal liver biochemistry. However, eight patients had abnormal liver enzymes but normal IVC and operative cholangiography.

There were no deaths in this series. Four postoperative complications occurred: two major and two minor (*Table 2*). A single intraoperative bile duct injury occurred in a patient with a gangrenous gallbladder. An operative cholangiogram was performed and was normal. After operation this patient developed jaundice and a subhepatic collection of bile was

Table 1 *Indications for laparoscopic cholecystectomy* (n = *100*)

Indication	No. of cases
Symptomatic cholelithiasis	68
Acute cholecystitis	15
Chronic cholecystitis	7
Gallstone pancreatitis	4
History of obstructive jaundice	3
Mucocele	2
Acalculous cholecystitis	1

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Table 2 *Postoperative complications* ($n = 4$)

Complication	Management
Bile duct injury	Choledochojejunostomy
Bile leak	Percutaneous drainage
Transient jaundice	Normal ERCP
Umbilical wound abscess	Drainage

ERCP, endoscopic retrograde cholangiopancreatography

drained percutaneously. Her jaundice did not improve and ERCP confirmed a common bile duct stricture which necessitated a Roux-en-Y choledochojejunostomy.

Discussion

Laparoscopic cholecystectomy is rapidly emerging as the treatment of choice for symptomatic gallstone disease. Its main advantages over open cholecystectomy seem to be cost containment, patient preference, and the ability of the patient to return to normal duties in a relatively short period of time. Laparoscopic cholecystectomy achieves the same end as open cholecystectomy, differing only in operative access. As yet the common bile duct is relatively inaccessible, so correct imaging of the bile duct is as much a concern with laparoscopic cholecystectomy as it is with open cholecystectomy.

The advantages of operative cholangiography are many. It will detect clinically unsuspected duct stones[8], may be used as a 'road map' to delineate the extrahepatic duct system, and may help to prevent bile duct injury[9,10]. The incidence of unsuspected stones determined by cholangiography is as high as 12 per cent[5,6], but this value can be questioned. In large series of open cholecystectomy without cholangiography[11,12], the reported incidence of symptoms from residual stones was as low as 0·3 per cent. The natural history of the majority of asymptomatic duct stones may be spontaneous passage; with safe ERCP and sphincterotomy[13,14] such a low percentage is acceptable.

The argument that ductal injuries can be prevented by routine operative cholangiography may also be invalid. Injury to the bile duct is mainly a technical problem and many strictures occur after inappropriate clamping or diathermy in the presence of bleeding. This should be prevented by careful technique and applies equally to laparoscopic cholecystectomy as to open cholecystectomy. Evidence from the recent literature suggests that a policy of selective cholangiography is more appropriate provided that certain clinical criteria are applied[15-17]. Abnormal liver biochemistry, history of jaundice or pancreatitis and a dilated common bile duct are all clinically reliable indicators of stones.

All of the patients in our study had preoperative IVC performed with tomography. The clarity of imaging of the ducts was excellent with IVC (*Figure 1*) and compared very favourably with operative cholangiography in the detection of stones. Recent studies[18-20] support these findings. IVC has been in use for many years but has fallen into disrepute because of poor imaging and an unacceptable incidence of allergic reactions. The contrast now used at the correct infusion rate[21] is hypoallergic in comparison with previous infusion regimens, and the quality of imaging that can be obtained in combination with tomography is very good.

In conclusion, laparoscopic cholecystectomy is now the method of choice in the management of gallstones. IVC is a safe and effective method of imaging the bile duct system before operation. Operative cholangiography during laparoscopic cholecystectomy should be reserved for selective use only and may be particularly helpful in patients where there is difficulty in demonstrating the anatomy of the cystic and main bile ducts.

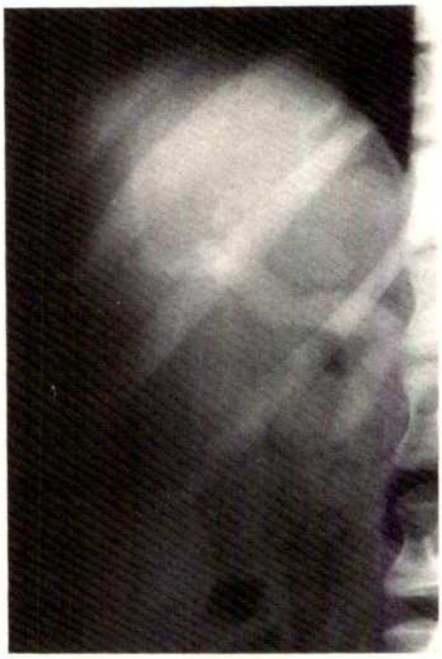

Figure 1 *Intravenous cholangiogram showing multiple stones in a dilated common bile duct and no flow into the duodenum*

References

1. Peters JH, Ellison EC, Innes JT *et al.* Safety and efficacy of laparoscopic cholecystectomy. An analysis of 100 initial patients. *Ann Surg* 1991; **213**: 3–12.
2. Reddick EJ, Olsen DO. Laparoscopic laser cholecystectomy. *Surg Endoscopy* 1989; **3**: 131–3.
3. Dubois F, Icard P, Berthelot G, Levard H. Coelioscopic cholecystectomy. *Ann Surg* 1990; **211**: 60–3.
4. Reddick EJ, Olsen DO. Outpatient laparoscopic laser cholecystectomy. *Am J Surg* 1990; **160**: 485–7.
5. Pagne TJ, Stahlgren LH. Indications and accuracy of operative cholangiography. *Arch Surg* 1980; **115**: 1214–15.
6. Schulenberg CAR. Operative cholangiography: 1000 cases. *Surgery* 1969; **65**: 723–30.
7. Dripps RD. New classification of physical status. *Anesthesiology* 1963; **24**: 111–17.
8. Jolly PC, Baker JW, Schmidt HM, Walker JH, Holm JC. Operative cholangiography: a case for its routine use. *Ann Surg* 1968; **104**: 484–8.
9. Cahill CJ, Pain JA. Current practice in biliary surgery. *Br J Surg* 1988; **75**: 1169–72.
10. Kelly CJ, Blumgart LH. Peroperative cholangiography and postcholecystectomy strictures. *Ann R Coll Surg Engl* 1985; **67**: 93–5.
11. Bartlett MK, Quinby WC. Mortality and complications of cholecystectomies and choledochostomy for chronic cholecystitis. *N Engl J Med* 1956; **254**: 154–6.
12. Gerber A, Apt MK. The case against routine operative cholangiography. *Am J Surg* 1982; **143**: 734–6.
13. Baille J, Cairns SR, Cotton PB, Putman WS. Endoscopic management of choledocholithiasis during pregnancy. *Surg Gynecol Obstet* 1990; **171**: 1–4.
14. Bilbao MK, Dotter CT, Lee TG, Katon RM. Complications of endoscopic retrograde cholangiopancreatography. *Gastroenterology* 1976; **70**: 314–20.
15. Pernthaler H, Sandbichler P, Schmid T, Margreiter R. Operative cholangiography in elective cholecystectomy. *Br J Surg* 1990; **77**; 399–400.
16. Hauer-Jensen M, Karesen K, Nygaard K *et al.* Consequences of routine peroperative cholangiography during cholecystectomy for gallstone disease. A prospective randomized study. *World J Surg* 1986; **10**: 996–1002.
17. Del Santo P, Kazarian KK, Rodgers JF, Bevins PA, Hall JR. Prediction of operative cholangiography in patients undergoing elective cholecystectomy with routine liver function chemistries. *Surgery* 1985; **98**: 7–11.

18. Daly J, Fitzgerald T, Simpson CJ. Pre-operative intravenous cholangiography as an alternative to routine operative cholangiography in elective cholecystectomy. *Clin Radiol* 1987; **38**: 161–3.
19. Huddy SP, Southam JA. Is intravenous cholangiography an alternative to the routine per-operative cholangiogram? *Postgrad Med J* 1989; **65**: 896–9.
20. Scott IR, Gibney RG, Becker CD, Fache JS, Burhenne HJ. The use of intravenous cholangiography in teaching hospitals: a survey. *Gastrointest Radiol* 1989; **14**: 148–50.
21. Nilsson U. Adverse reactions to iotroxate at intravenous cholangiography. A prospective clinical investigation and review of the literature. *Acta Radiol* 1987; **28**: 571–5.

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Short note

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Effect of donor pre-treatment with anti-lymphocyte globulin on small bowel transplantation in rats

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Poor clinical results of intestinal transplantation reflect difficulties in achieving adequate immunosuppression in the recipient. The small bowel allograft is highly immunogenic, in large part due to the rich lymphoid load of the lamina propria. A possible approach to reducing the lymphocytic load of the graft would be by pre-treating it with anti-lymphocyte globulin (ALG) or specific monoclonal antibodies directed against lymphocytes. Donor pre-treatment with cytotoxic drugs or ALG has been shown to prolong the functional survival of renal and cardiac allografts[1,2]. The aim of this study, therefore, was to investigate the effect of ALG donor pre-treatment upon intestinal allograft survival in a rat model of small bowel allograft involving disparate rat strains to ensure a high incidence of rejection.

Methods

Orthotopic small intestinal grafts were performed between adult Brown Norway (BN) and Lewis rats. All rats weighed between 250 and 350 g. In the donor animal, 20 cm of proximal small bowel was isolated, preserving the superior mesenteric artery and vein. The duodenum and pancreas were dissected free from the portal vein, and the left gastric and splenic branches were ligated and divided. The aorta distal to the origin of the superior mesenteric artery was divided and doubly ligated, and proximal aortic branches (right renal, lumbar and coeliac) were ligated and divided. The graft was excised by dividing the aorta at the level of the coeliac axis and the portal vein as high as possible within the porta hepatis. The graft was cooled with saline at 4°C and was perfused via the aortic stump with cold heparinized Ringer's lactate. The recipient inferior vena cava and aorta were identified and clamped. End-to-side anastomoses were performed between graft portal vein and inferior vena cava and the graft aortic stump and recipient infrarenal aorta respectively, using 10/0 nylon suture.

Native bowel (20 cm) was excised after ligating the mesenteric vessels. The graft was anastomosed in continuity with the divided native bowel with a single continuous layer of 7/0 silk sutures. Fluid replacement was administered by intravenous injection of 2 to 8 ml Ringer's lactate into the dorsal vein of the penis and by subcutaneous injection of 10 ml Ringer's lactate at the end of the procedure. Animals were allowed free access to chow and water and were inspected and weighed daily. All animals were treated according to guidelines established by the Animal Care Committee and Research Animal Resources of the University of Minnesota. The perioperative mortality rate from technical failure was 9 per cent (four of 44 animals).

Seven groups of animals were studied using the following donor/recipient combinations: (1) BN/BN (isograft control); (2) BN/Lewis (untreated allograft control); (3) BN graft pre-treated by *ex vivo* flushing with heparinized saline containing 1 ml goat anti-rat ALG (42·7 mg protein/ml) into Lewis; (4) BN pre-treated with two 1 ml doses of anti-rat ALG by intraperitoneal injection, 48 h and 24 h before harvesting, grafted into Lewis; (5) BN grafted into Lewis treated with cyclosporin A (15 mg/kg/day) by intramuscular injection for 10 days after grafting; (6) BN grafted into Lewis treated with cyclosporin A (2 mg/kg/day) by intramuscular injection for 10 days after grafting; (7) BN donor pre-treated with two 1 ml doses of goat anti-rat ALG by intraperitoneal injection, 48 h and 24 h before harvesting the graft, Lewis recipient treated with cyclosporin A (2 mg/kg/day) by intramuscular injection for 10 days after grafting.

Histological sections of bowel from ALG-treated animals were examined by immunohistochemistry. Formalin-fixed paraffin sections were incubated with biotinylated rabbit anti-goat serum, avidin-biotin horseradish peroxidase complex, and hydrogen peroxide plus 3,3-diaminobenzidine (Pierce Immunotechnology, Rockford, Illinois, USA). Specific binding of the goat anti-rat ALG to lamina propria lymphocytes was confirmed by applying the ALG directly to formalin-fixed paraffin sections of untreated rat bowel and staining using the immunoperoxidase technique. Sections were counter-stained with methylene blue. Cells which bound ALG were stained brown. Statistical comparison of differences in survival was accomplished by use of the Mann–Whitney *U* test.

Results and discussion

The survival of the rats in each of the seven study groups is shown in *Table 1*. There was no difference in survival between untreated control rats and rats receiving a graft flushed with ALG (group 3) or a graft from a BN rat pre-treated at 48 h and 24 h with ALG (group 4). Immunosuppression with cyclosporin A at a dose of 15 mg/kg/day, however, significantly prolonged survival compared with untreated rats (group 5, $P = 0{\cdot}001$). Interestingly, even low doses of cyclosporin A (2 mg/kg/day) resulted in significant prolongation in survival compared with untreated animals (group 6, $P = 0{\cdot}02$). However, survival of animals treated with this low dose was significantly shorter than when higher doses of cyclosporin A (15 mg/kg/day) were used ($P = 0{\cdot}002$). Survival in Lewis rats treated with low doses of cyclosporin A (2 mg/kg/day) that received a small bowel allograft from BN rats pre-treated at 48 h and 24 h with ALG was significantly prolonged compared with rats treated with low doses of cyclosporin A (2 mg/kg/day) that received a graft from untreated BN rats (group 7, $P = 0{\cdot}004$). Post-mortem examination of all the rats which died showed a distended, thickened, disorganized graft without peritonitis and normal native bowel, consistent with rejection of the graft.

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Table 1 *Outcome of allograft after different treatments*

Group	Donor rat	Recipient rat	Donor treatment	Recipient treatment	*n*	Survival (days)	Mean(s.d.)
1	BN	BN	None	None	5	216,282,302,314,316	Killed
2	BN	Lewis	None	None	6	8,9,10,10,12,13	10·0(1·91)
3	BN	Lewis	ALG flush	None	8	5,7,7,8,8,9,11,21	9·5(4·63)
4	BN	Lewis	Intraperitoneal ALG*	None	5	7,8,8,10,11	8·8(1·46)
5	BN	Lewis	None	CSA 15 mg/kg/day	6	23,25,26,30,32,32	28·0(3·51)
6	BN	Lewis	None	CSA 2 mg/kg/day	5	10,15,16,17,19	15·4(3·01)
7	BN	Lewis	Intraperitoneal ALG*	CSA 2 mg/kg/day	5	22,22,23,24,36	25·4(5·35)

* Injections carried out 48 h and 24 h before graft harvesting. BN, Brown Norway; ALG, anti-lymphocyte globulin; ALG flush, graft flushed *ex vivo* with 1 ml ALG; CSA, cyclosporin A

These studies demonstrate that cyclosporin A treatment successfully prolongs survival after orthotopic small bowel allograft in the rat. However, long-term survival was not observed, in contrast to the findings of other authors who have obtained long-term survival with similar regimens[3–5]. Pre-treatment of the graft with ALG by flushing the vascular pedicle had no effect on survival. Other attempts at reducing the lymphoid load of intestinal grafts by irradiation or excision of mesenteric nodes have not been associated with prolongation of graft survival in rats[6,7], although graft *versus* host disease is reduced in models which use strain combinations in which this phenomenon predominates.

Although donor pre-treatment with ALG did not prolong survival, when ALG pre-treatment was combined with low doses of cyclosporin A treatment, an additive effect occurred which produced a significant increase in survival. We hypothesize that donor pre-treatment with ALG altered the immunogenicity of the graft. However, it was not possible to demonstrate binding of ALG to graft lamina propria lymphocytes by immunohistochemistry using biopsies taken after ALG pre-treatment, despite binding of ALG to lymphocytes when applied directly to histological sections of rat small bowel.

In conclusion, we believe that this series of experiments suggests that combination treatment with donor pre-treatment and recipient immunosuppression may improve survival of intestinal allografts.

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References

1. Guttmann RE, Lindquist R. Renal transplantation in the inbred rat. Reduction of allograft immunogenicity by cytotoxic drug pre-treatment of donors. *Transplantation* 1969; **8**: 490–5.
2. Freeman JS, Chamberlain EC, Reemtsma K, Steinmuller D. Prolongation of rat heart allografts by donor pre-treatment with immunosuppressive agents. *Transplant Proc* 1971; **3**: 580–2.
3. Kirkman RL, Lear PA, Madara JL, Tilney NL. Small intestinal transplantation in the rat – immunology and function. *Surgery* 1984; **96**: 280–6.
4. Lee KKW, Schraut WH. Structure and function of orthotopic small bowel allografts treated with cyclosporin. *Am J Surg* 1986; **151**: 55–60.
5. Harmel RP, Staney M. Improved survival after allogenic small intestinal transplantation in the rat using cyclosporin immunosuppression. *J Pediatr Surg* 1986; **21**: 214–17.
6. Schraut WH. Current status of small bowel transplantation. *Gastroenterology* 1988; **94**: 525–38.
7. Gundlach M, Schroeder P, Hansmann ML *et al.* Graft manipulation prior to small intestinal transplantation. *Transplant Proc* 1989; **21**: 2894–5.

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Ultrasonography in the acute abdomen

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In a prospective study 152 consecutive patients presenting with acute abdominal pain were assessed clinically and an ultrasonographic examination was performed immediately. Of these, 16 (11 per cent) patients would normally have had an immediate ultrasonographic scan requested; routine (within 24 h of admission) ultrasonographic examination would have been requested in a further 66 (43 per cent) patients. In 70 (46 per cent) patients an ultrasonographic examination would not have been requested. Ultrasonography altered the diagnosis in one patient from probable appendicitis to cholecystitis. Ultrasonography missed one abdominal aortic aneurysm and one empyema of the gallbladder. Ultrasonography had a sensitivity of 96 per cent, a specificity of 94 per cent, a positive predictive value of 96 per cent, a negative predictive value of 94 per cent and an accuracy of 95 per cent in diagnosing appendicitis. Exactly the same values were found for the clinical diagnosis of appendicitis. The study shows that routine immediate ultrasonographic examination of the acute abdomen is rarely helpful, with the possible exception of appendicitis. Where an urgent ultrasonographic scan is necessary on clinical grounds the expertise of a radiologist is probably required, whereas in specific areas, for example in the diagnosis of right iliac fossa pain, there may be a place for training the surgical trainee.

Ultrasonography is a well established non-invasive method for the investigation of the abdomen, because of its high degree of accuracy, non-invasiveness and low cost[1–4]. Its accuracy in the assessment of the acute abdomen with special reference to appendicitis is controversial[5]. In view of the development of portable ultrasonography machines and the notion that perhaps surgical trainees ought to be proficient in the technique[3,4], we have assessed the usefulness of immediate ultrasonographic examination in the clinical management of patients referred with acute abdominal pain, in an attempt to ascertain the effect of ultrasonography on clinical management and to see whether there is a need to train surgeons in all aspects of abdominal ultrasonography.

Patients and methods

In all, 152 consecutive patients, 84 men and 68 women of mean age 52 years (range 1–94 years), with acute abdominal pain were studied. They were initially assessed by either the surgical registrar or senior registrar on-take, who completed the proforma shown in *Table 1*. The proforma ensured that the doctors concerned had formulated a management plan; they were requested to state whether they felt the ultrasonographic examination would be requested immediately, as a routine examination (within 24 h of admission), or would not normally be requested. After the clinical assessment an abdominal ultrasonographic scan was performed by an experienced radiologist using an ATL Mark 8 (Advanced Technology Laboratories Ltd., Letchworth, UK) or Acuson 128 (Acuson Computed Sonography Ltd., Stevenage, UK) ultrasound scanner. These findings were incorporated into the proforma sheet. The results were then made available to the surgeon to ascertain whether the ultrasonographic examination would affect the initial treatment of the patients. For the purpose of the trial the final diagnosis was that made by the consultant in charge of the patient at the time of discharge.

Results

Ultrasonography was used to investigate 152 patients. Sixteen (11 per cent) patients would normally have required an immediate ultrasonographic examination; 66 (43 per cent) would have undergone a routine ultrasonographic examination within the following 24 h. In 70 (46 per cent) patients ultrasonography would not have been requested to aid the clinical management. *Table 2* summarizes the initial presumptive site of suspected pathology/clinical diagnosis and the allocation of these patients into groups with respect to their predicted need for ultrasonographic examination. *Table 3* lists the final diagnoses in these patients and the number in whom diagnosis was confirmed by ultrasonography.

In the 16 patients in whom an immediate ultrasonographic examination would normally have been requested, clinical management was aided by the results of this investigation. In only one other patient (1 per cent), in whom a diagnosis of probable appendicitis was changed to cholecystitis, was initial management changed from admission with clinical review 4 h later to admission and immediate antibiotic therapy. Therefore 17 (11 per cent) patients benefited from immediate ultrasonographic examination.

Ultrasonographic examination missed one leaking abdominal aortic aneurysm and one empyema of the gallbladder. The former was diagnosed at laparotomy in a 94-year-old patient. Repair of the aneurysm was not attempted and he died 2 days later. His initial clinical diagnosis was peritonitis of unknown cause. The ultrasonographic scan visualized the patient's aorta

Table 1 *Ultrasonographic management of the acute abdomen: information recorded for each patient*

Name	
Age	
Sex	
Diagnosis	
Differential diagnosis	
Management plan	
Ultrasonography result	
Did ultrasonographic examination change management?	(Yes/no)
Final diagnosis at discharge	

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Table 2 *Initial site of suspected pathology/clinical diagnosis and allocation of patients into groups with respect to predicted need for ultrasonographic examination*

	No. of patients	Percentage of all cases
Patients who would have required immediate ultrasonography ($n = 16$)		
Trauma	5 (31)	3
Abdominal aortic aneurysm	6 (38)	4
Ectopic pregnancy	3 (19)	2
Intussusception	1 (6)	1
Renal failure	1 (6)	1
Patients who would have required routine ultrasonography ($n = 66$)		
Biliary/pancreatic	21 (32)	14
Genitourinary	17 (26)	11
Colon	6 (9)	4
Non-specific abdominal pain	8 (12)	5
Gynaecological	8 (12)	5
Other	6 (9)	4
Patients in whom routine ultrasonography would not have been requested ($n = 70$)		
Non-specific abdominal pain	21 (30)	14
Colon	6 (9)	4
Small bowel	7 (10)	5
Appendicitis	24 (34)	16
Other	12 (17)	8

Values in parentheses are percentages

Table 3 *Final diagnoses in 152 patients and the number in whom the final diagnosis was confirmed by ultrasonography*

	No. of patients	Final diagnosis	US
Patients who would have required immediate ultrasonography ($n = 16$)			
Trauma	3	Renal contusion	
	1	Ruptured spleen	1
	1	Fractured 12th rib	
Abdominal aortic aneurysm	2	Abdominal aortic aneurysm	1
	1	Diverticular disease	
	2	Myocardial infarction	
	1	Cerebrovascular accident	
Ectopic pregnancy	2	Non-specific abdominal pain	
	1	ND (negative appendicectomy)	
Intussusception	1	Intussusception	1
Renal failure	1	Benign prostatic hypertrophy	1
Patients who would have required routine ultrasonography ($n = 66$)			
Biliary/pancreatic	7	Cholecystitis	7
	5	Biliary colic	5
	2	Pancreatic carcinoma	2
	2	Empyema of gallbladder	1
	1	Pancreatitis	
	4	ND	
Genitourinary	6	Renal colic	4
	4	Infection	2
	3	Carcinoma of prostate	1
	2	Bladder tumours	2
	2	Retention	2
Colon	3	Diverticular disease	3
	2	Inflammatory bowel disease	
	1	Gallstones	1
Non-specific abdominal pain	8	ND	
Gynaecological	3	Ovarian carcinoma	3
	2	Ovarian cyst	2
	1	Tubo-ovarian abscess	1
	1	Pelvic inflammatory disease	
	1	ND	
Other	1	Gastric carcinoma	1
	1	Sickle cell crisis	
	1	Disseminated carcinoma	1
	1	Empyema of gallbladder	1
	2	ND	
Patients in whom routine ultrasonography would not have been requested ($n = 70$)			
Non-specific abdominal pain	21	ND	
Colon	2	Constipation	
	2	Inflammatory bowel disease	
	1	Carcinoma of colon	
	1	Cholecystitis	1
Small bowel	2	Inguinal hernia	
	3	Crohn's disease	
	1	Coeliac disease	
	1	Pseudo-obstruction	
Appendicitis	23	Appendicitis	21
	1	Negative appendicectomy	
Other	2	Gastroenteritis	
	1	Pouchitis	
	2	Diverticular disease	
	7	ND	

ND, no diagnosis at the time of discharge; US, ultrasonographic diagnosis confirmed the clinical diagnosis

poorly and no accurate assessment was possible, partly because he was unable to remain still. In the second case the ultrasonographic scan showed a normal gallbladder containing some sludge.

In patients with right iliac fossa pain, the decision of whether to proceed to appendicectomy was made before the surgeon was aware of the result of the ultrasonographic examination, and no decision was reversed in spite of the ultrasonography report. Of 41 patients with right iliac fossa pain and appendicitis as a possible differential diagnosis, 25 patients had an appendicectomy and 23 were confirmed histologically as having appendicitis. Ultrasonography correctly diagnosed appendicitis in 21 patients. In the two patients who underwent a negative appendicectomy, ultrasonography had shown the features of appendicitis in a woman at 14 weeks' gestation and in the other case the ultrasonographic scan had been normal.

Initial clinical assessment and ultrasonographic examination had the same sensitivity (96 per cent), specificity (94 per cent), positive predictive value (96 per cent), negative predictive value (94 per cent) and accuracy (95 per cent) in the prediction of appendicitis.

Sixty-five (43 per cent) patients had their clinical diagnosis confirmed by ultrasonography. In patients in whom a routine ultrasonographic scan would have been requested, 39 (59 per cent) had an ultrasonographic examination that confirmed the initial clinical diagnosis. In those in whom an ultrasonographic examination would not have been requested, only 22 (31 per cent) patients had a diagnosis made on ultrasonography and in only one (1 per cent) patient was the diagnosis changed. In the group requiring immediate ultrasonography, only three (19 per cent) patients had their initial possible diagnosis confirmed.

During the ultrasonographic examinations no asymptomatic intra-abdominal pathology that required treatment was found.

Discussion

It has been suggested that patients with an acute abdomen should have an ultrasonographic examination performed by the admitting surgeon[3,4]; small portable machines have become available to make this easier. No assessment has been made of whether early ultrasonography might influence patient management. Parys *et al.*[4] have shown that equivalent results for abdominal ultrasonography can be obtained by surgical trainees and radiologists, but they did not address the question as to the effect of ultrasonography on the management of patients with an acute abdomen. This study was designed to see whether immediate ultrasonographic examination could improve patient management. If this were the case, there might be a need to train surgical staff in ultrasonography.

This study shows that in only 11 per cent of patients was the immediate management influenced by ultrasonographic examination. In the group of patients in whom an immediate ultrasonographic scan would normally have been requested, the main function of the scan was to exclude serious surgical pathology which required immediate intervention. Eighty-eight per cent of the patients in whom an immediate ultrasonographic examination would have been requested presented with trauma, a suspected aortic aneurysm or ectopic pregnancy.

The overall confirmation rates of the clinical diagnosis by ultrasonography are similar to those for previously reported data[6]. In patients with right iliac fossa pain, ultrasonographic examination is non-invasive and in expert hands has as good a detection rate of appendicitis as laparoscopy[5]. Furthermore, ultrasonography allows an assessment of the rest of the abdomen and, unlike laparoscopy, there are no contraindications such as previous laparotomies, and the procedure does not involve the need for general anaesthesia. In our study the figures for the ultrasonographic detection of appendicitis were similar to those in other series[7–9]. However, they were no better than the clinical diagnosis of the admitting surgeon. The high level of clinical accuracy may be related to the fact that the most junior person making the acute clinical diagnosis had at least 2 years experience after gaining the fellowship of the Royal College of Surgeons.

Should all surgical trainees be taught the technique of general abdominal ultrasonography? Undoubtedly ultrasonography can be learnt by surgeons[3,4] and may be reliable in specific areas such as biliary disease and right iliac fossa pain. However, Parys *et al.*[4] acknowledge that 'equivocal scans should be repeated by the radiologist'. In view of the fact that there is a wide variety of possible pathologies that need to be excluded in this group of patients, we feel that a radiologist is probably the best person to perform these urgent examinations. Furthermore, as only 11 per cent of patients required an immediate ultrasonographic examination, the radiology department is not put under an excessive burden.

In conclusion, ultrasonography is rarely a useful adjunct to clinical diagnosis in the immediate management of the acute abdomen. In only a small number of patients does ultrasonographic examination influence the initial management of the patient. In view of this small number it does not seem to be an appropriate use of resources to issue portable ultrasonography machines to all surgical trainees and train them in general ultrasonographic examination of the abdomen. The ultrasonographic examination in these patients is probably better performed by a radiologist.

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References

1. Cooperberg PL, Burhenne HJ. Real time ultrasonography. Diagnostic technique of choice in calculous gall bladder disease. *N Engl J Med* 1980; **302**: 1277–9.
2. Morgensen NB, Madsen M, Stage P *et al.* Ultrasonography *versus* roentgenography in suspected instances of cholelithiasis. *Surg Gynecol Obstet* 1984; **159**: 353–6.
3. Griffiths C. Ultrasound and laparoscopy in surgery. *Br J Hosp Med* 1989; **42**: 173.
4. Parys BT, Barr H, Chantarsak *et al.* Use of ultrasound scan as a bedside diagnostic aid. *Br J Surg* 1987; **74**: 611–12.
5. Hoffmann J, Rasmussen OO. Aids in the diagnosis of acute appendicitis. *Br J Surg* 1989; **76**: 774–9.
6. Carmody E, McGrath FP, Keeling F. The role of emergency ultrasonography in the management of the acute abdomen. *Br J Radiol* 1990; **63**: 383.
7. Puylaert JBCM, Rutgers PH, Laisang RI *et al.* A prospective study of ultrasonography in the diagnosis of appendicitis. *N Engl J Med* 1987; **317**: 666–9.
8. Scherk WB, Wichtrup B, Ruschoff J, Rothmund M. Acute and perforated appendicitis: current experience with ultrasound-aided diagnosis. *World J Surg* 1990; **14**: 271–6.
9. Adams DH, Fine C, Brooks DC. High-resolution real-time ultrasonography: a new tool in the diagnosis of acute appendicitis. *Am J Surg* 1988; **155**: 93–7.

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Prospective randomized trial of Nissen fundoplication and Angelchik prosthesis in the surgical treatment of medically refractory gastro-oesophageal reflux disease

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Fifty patients with gastro-oesophageal reflux disease refractory to multiple courses of medical therapy were entered into a prospective randomized trial comparing Nissen fundoplication with the Angelchik prosthesis as a primary surgical procedure. The two groups were matched for age, sex, duration of symptoms before surgery, type of medical therapy, pattern of symptom presentation, endoscopic grade of oesophageal inflammation, manometric lower oesophageal pressure and 24-h pH profile. Twenty-five patients were randomized to each of the Nissen fundoplication and Angelchik prosthesis groups. Operation time and hospital stay were similar in both groups. Persistent dysphagia was reported in five of the patients with an Angelchik prosthesis compared with none in the Nissen fundoplication group. Three prostheses were removed because of severe dysphagia while no Nissen fundoplication required revision. No patient with preoperative dysphagia because of stricture reported swallowing difficulties after operation. At clinical assessment at 3, 6, 12 and 24 months after operation, 85–88 per cent of the patients having a Nissen fundoplication were graded Visick 1 or 2 compared with 60–72 per cent of patients in the Angelchik group.

Most patients with gastro-oesophageal reflux disease can be successfully managed with medical treatment alone[1]. However, in patients with reflux disease which is unresponsive to medical therapy, surgical treatment remains problematical[2]. The multiplicity of different anti-reflux procedures indicates that the ideal operation for this condition has not been established. Furthermore, advances in the surgical treatment of reflux are hindered by a relatively poor understanding of the mechanisms of reflux control and by the difficulties in comparing the efficacy of one surgical procedure with another using retrospective data alone[3].

The Nissen fundoplication remains the most commonly performed operation for reflux disease[2]. However, fundoplication has a success rate of 80 to 85 per cent which is operator-dependent, and it may be complicated by recurrent reflux symptoms, dysphagia and the gas-bloat syndrome[4]. The Angelchik prosthesis was introduced as a simple alternative procedure[5] to overcome these problems.

To evaluate the role of the Angelchik prosthesis in the surgical treatment of reflux disease, we have conducted a prospective randomized trial of the prosthesis against the Nissen fundoplication. This interim analysis was carried out to confirm the impression that the complication rate was higher and functional outcome significantly inferior following the Angelchik operation.

Patients and methods

All patients were assessed before operation by the operating surgeon (J.G.T.). Admission criteria to the study allowed only those patients with persistent symptoms of reflux unresponsive to multiple courses of medical therapy and without previous attempts at anti-reflux surgery to be included. Diagnosis was confirmed following clinical evaluation by barium swallow, flexible upper gastrointestinal endoscopy and 24-h pH studies in each case. Oesophageal manometry was also performed in each patient to exclude those with primary motility disorders in whom anti-reflux surgery may be inappropriate.

Ten patients also underwent 24-h pH studies at an interval of 3–6 months after operation. Bread barium swallow studies were performed in those patients who complained of dysphagia following surgery.

Manometry was performed using a five-lumen polyvinyl flexible catheter perfused with water at 0·5 ml/min using a low compliance pneumohydraulic system. Intraluminal pressure was transmitted via external transducers and recorded on a multichannel pen recorder. Three of the five side holes were located 5 cm from the distal end of the catheter and positioned 120° radially to one another. The other two side holes were positioned 10 and 15 cm from the distal end of the catheter. The catheter was inserted through the nares in the fasted patient and passed into the stomach. Using a station pullthrough technique the catheter was withdrawn at 1 cm intervals until the high pressure zone was located at the respiratory reversal point in the distal oesophagus. The lower oesophageal sphincter pressure was recorded as previously described[6] with the patient semi-recumbent.

After withdrawal of the manometry catheter, an antimony-tipped pH electrode (Synectics Medical AB, Stockholm, Sweden) was positioned 5 cm above the manometrically defined lower oesophageal high pressure zone. Intra-oesophageal pH was recorded for 24 h on a portable solid state Digitrapper (Synectics Medical AB) with the patient ambulant. The pH data were off-loaded, stored and analysed on a computer using Synectics software. The total time spent at $\text{pH} < 4{\cdot}0$ was analysed as a percentage of the total study period.

Patients were randomized at the time of surgery to receive either an Angelchik prosthesis or a Nissen fundoplication. All operations were performed by one consultant surgeon (J.G.T.) who had extensive previous experience of both procedures. All operations in this study were carried out through a vertical midline incision. After division of the left triangular ligament of the liver, the oesophagus was mobilized by a combination of blunt and sharp dissection until 5 cm was clear. A crural repair was carried out in those patients whose oesophageal hiatus admitted more than two fingers after reduction of any hiatus hernia, by using three interrupted no. 1 silk sutures. Care was taken to avoid damage to the vagal nerve trunks and to the spleen.

In those patients who received an Angelchik prosthesis, mobilization

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Table 1 *Patient symptoms before operation and type of medical therapy in the two groups**

	Nissen ($n = 25$)	Angelchik ($n = 25$)
Symptom		
Heartburn	22	23
Acid regurgitation	20	21
Dysphagia (stricture)	4	2
Medical therapy		
Antacids	25	25
H_2 blockers	25	25
Omeprazole	12	10

* Differences between the two groups were not statistically significant

of the gastric fundus was not carried out. After placing the silicone collar around the mobilized oesophagus and securely tying the reinforced Dacron® (DuPont, Wilmington, Delaware, USA) tapes of the device, the knot was transfixed using a no. 1 silk ligature and clipped with a heavy metal Ligaclip (Ethicon, UK).

In the group undergoing Nissen fundoplication, the fundus of the stomach was mobilized with division of the upper short gastric vessels. The fundus was then wrapped behind the mobilized oesophagus and approximated to the anterior surface of the upper lesser curve using two interrupted no. 1 silk sutures to anchor the wrap laterally, and a further no. 1 silk suture inferiorly. All fundoplications were carried out with a no. 16 Fr nasogastric tube and a 44 Fr Maloney dilator placed in the oesophageal lumen to ensure a 'floppy' wrap of 3 cm.

All patients received full prophylaxis against deep vein thrombosis using subcutaneous heparin and anti-embolism stockings in the immediate preoperative period and, after operation, until fully mobile. Postoperative functional outcome was determined by an independent clinical practitioner.

As the data were not normally distributed, differences in interval data were analysed using the Wilcoxon rank two-sample test. Categorical data were analysed using the χ^2 test with Yates continuity correction or Fisher's exact test as appropriate. A sample size of 100 patients was determined as necessary to demonstrate a 20 per cent difference in functional outcome between the two groups with 80 per cent study power at the five per cent significance level.

Results

Fifty patients have so far been recruited to the study, with 25 patients in each of the Nissen fundoplication and Angelchik prosthesis groups.

Before operation

There was no significant difference in age between the two groups (Nissen: median 50 years, range 27–67 years *versus* Angelchik: median 44 years, range 30–67 years). The sex distribution was also similar (Nissen: male:female 14:11 *versus* Angelchik: male:female 16:9). Symptom duration before surgery was no different in the two groups (Nissen: median 3·4 years, range 1·7–18·6 years *versus* Angelchik: median 3·8 years, range 1·4–20·5 years). The pattern of symptom presentation was similar in the two groups, as was the type of medical therapy given (*Table 1*). The groups were matched for endoscopic grade of oesophageal inflammation, manometric lower oesophageal sphincter pressure and 24-h pH profile (*Table 2*).

Operation

The operative time was similar in both groups (Nissen: median 50 min, range 35–95 min *versus* Angelchik: median 50 min, range 25–65 min). Hospital stay was identical in both groups (median 8 days, range 6–15 days).

One patient in each group had had previous vagotomy and pyloroplasty. One patient in each group had had a highly selective vagotomy performed and a further patient in each group underwent cholecystectomy at the time of the anti-reflux operation. Care was taken to divide the minimum number of short gastric vessels to achieve a satisfactory Nissen wrap in the patient who had also had a highly selective vagotomy. No patient required splenectomy.

After operation

Complications. One patient in each group developed a pulmonary embolus in the first week after operation: both patients made a full recovery. A further two patients in the Nissen fundoplication group and three in the Angelchik prosthesis group developed chest infections while in hospital. All made satisfactory recoveries following active physiotherapy and antibiotics. One patient in the Nissen group had a transient episode of melaena owing to an erosive gastritis, which settled on conservative treatment with ranitidine.

Complications specific to anti-reflux surgery were more than twice as common in the Angelchik prosthesis group. Dysphagia was reported as a significant persistent problem in five members (20 per cent) of this group while one other patient with a Nissen fundoplication reported mild transient dysphagia with solid food. Bread barium swallow studies in these six patients showed gastro-oesophageal junction obstruction in the five with an Angelchik prosthesis, but the single patient with a Nissen fundoplication who developed temporary mild dysphagia had a normal radiological result.

Endoscopy showed a significant oesophageal narrowing in three of the five affected patients in the Angelchik group. These three patients required reoperation and removal of the prosthesis because of severe persistent dysphagia with liquids and solids. The prosthesis was found encapsulated in a dense fibrous mass which was compressing the lower oesophagus in two patients and the upper stomach in one.

No patient with preoperative dysphagia or a stricture in either group had swallowing problems after operation. The only patient in this series to develop the gas-bloat syndrome[6] was in the Nissen fundoplication group. The symptoms settled after 3 months.

Table 2 *Endoscopic oesophageal appearance, barium swallow, oesophageal manometric pressure and 24-h pH data in the two groups**

	Nissen ($n = 25$)	Angelchik ($n = 25$)
Endoscopy		
Inflammation	25	25
Ulceration	14	15
Barium studies		
Free reflux	25	25
Oesophageal manometry		
Lower oesophageal sphincter pressure (mmHg)†	12(5–35)	15(5–30)
24-h pH studies		
Percentage of time at pH < 4†	15·6(3·2–47·6)	12·7(3·8–51·4)

* Differences between the two groups were not statistically significant.
† Values are median (range)

Table 3 *Functional outcome (Visick) in the two groups from 3 months to 2 years after operation. Results are expressed as patient outcome/patients available for study, at the various time intervals**

Time after operation (months)	Good result (Visick 1 and 2)		Poor result (Visick 3 and 4)	
	Nissen	Angelchik	Nissen	Angelchik
3	22/25	18/25	3/25	7/25
6	19/22	16/23	3/22	7/23
12	17/20	14/20	3/20	6/20
24	7/8	6/10	1/8	4/10

* Differences between the two operative procedures were not significant

Table 4 *Visick grades and 24-h pH profiles (expressed as percentage of time at pH < 4) in 16 patients before and after operation*

Nissen ($n = 7$)				Angelchik ($n = 9$)			
Preoperative		Postoperative		Preoperative		Postoperative	
Visick grade	Percentage of time at pH < 4	Visick grade	Percentage of time at pH < 4	Visick grade	Percentage of time at pH < 4	Visick grade	Percentage of time at pH < 4
4	26·0	1	0·7	4	8·7	1	0·1
4	7·1	1	2·7	4	44·6	1	39·4
4	21·2	1	11·4	4	9·6	1	0·6
4	9·7	1	1·2	4	19·0	1	1·5
4	29·0	1	3·3	4	7·7	1	0·6
4	8·2	1	0·7	4	9·1	1	0·5
4	8·7	1	3·4	4	19·9	1	20·8
				4	39·9	1	31·4
				4	23·6	1	10·4

Two patients in the Angelchik group developed recurrent reflux symptoms, as did one patient in the Nissen group. All three had recurrent oesophageal inflammation, seen on endoscopy, which required medical therapy. None of the above differences achieved statistical significance.

Functional outcome (*Table 3*). Of the patients in the Nissen fundoplication group, in the first 2 years after operation, 85–88 per cent were either symptom-free (Visick 1) or had occasional mild symptoms which did not require treatment (Visick 2). In contrast, 60–72 per cent of patients with an Angelchik prosthesis were graded Visick 1 or 2.

The seven patients with poor results (Visick 3 or 4) in the Angelchik group had either dysphagia (five) or recurrent reflux (two). The three patients with poor results in the Nissen group had dysphagia (one), recurrent reflux symptoms (one) or the gas-bloat syndrome (one). None of these differences achieved statistical significance.

24-h pH studies after operation (*Table 4*). The 16 patients who underwent 24-h pH testing before and after operation were graded Visick 4 before and Visick 1 after surgery. There were nine patients with an Angelchik prosthesis and seven patients with a Nissen fundoplication. The percentage of time at pH < 4 decreased in all but one of these 16 patients after operation. However, in five patients, a percentage of time at pH < 4 of more than 10 per cent was associated with an excellent functional result (Visick 1).

Discussion

These results suggest that the functional outcome after operation is superior with the Nissen fundoplication compared with the Angelchik prosthesis for up to 2 years. Five patients with an Angelchik prosthesis developed severe persistent dysphagia and this was significant enough to warrant removal of prosthesis in three. By contrast, no patient who underwent Nissen fundoplication developed severe dysphagia or required reoperation.

The study was analysed early because of a subjective impression that patients with an Angelchik prosthesis were having a worse outcome than those with a Nissen fundoplication. The results presented here confirm that impression, although statistical significance was not reached because of small sample size[7] and short follow-up. Despite these results being statistically inconclusive, we feel that the differences shown are clinically important and feel unable to randomize patients further to a procedure for which interim results have undermined clinical confidence.

Other studies have also shown that dysphagia occurs in over 20 per cent of patients following Angelchik prosthesis insertion[8,9], despite effective control of gastro-oesophageal reflux. In one small series the dysphagia was a transient early occurrence which improved on later review[10]. However, a recent prospective randomized trial of Nissen fundoplication and the Angelchik prosthesis[6], with a mean follow-up of 38 months (range 18–56 months), has shown a much less favourable outcome in the prosthesis group, especially regarding dysphagia.

It is possible that fibrous capsule formation around the Angelchik prosthesis, without any sign of intraperitoneal sepsis or prosthesis erosion into the stomach or oesophagus[11], may have accounted for the dysphagia in the present series[12]. It is possible that despite the relative biological inertness of silicone, insertion of the Angelchik prosthesis into the abdomen may result in a marked inflammatory reaction. Although one of the Angelchik prostheses migrated for a short distance distally because of a faulty tape, no proximal migration into the chest occurred in the present series, probably because of the crural repair.

The inaccuracy of 24-h pH studies in predicting functional outcome was illustrated by the five patients with an excellent outcome and associated abnormally high index of acid reflux. These observations confirm the findings of others[13] that 24-h pH studies are not accurate in this context.

This study adds to the growing evidence that, despite its ease of insertion, the high incidence of complications with the Angelchik prosthesis means it cannot be recommended for routine use in anti-reflux surgery. We feel that the choice between the Nissen fundoplication and the Angelchik prosthesis is no longer uncertain on clinical grounds[14]. Although interim analyses are prone to exaggerate differences between treatments[15], we feel that further randomization is unethical and the trial has been stopped. Use of the Angelchik prosthesis has been abandoned.

References

1. Polk HC, Zeppa R. Fundoplication for uncomplicated hiatal hernia. *Ann Thorac Surg* 1969; **7**: 202–5.
2. Cuschieri A. Surgical treatment of reflux disease. In: Hennessy TPJ, Cuschieri A, Bennett JR, eds. *Reflux Oesophagitis*. London: Butterworth, 1989: 143–69.
3. DeMeester TR, Fuchs KH. Long term results of medical and surgical therapy: surgical perspective. In: Starling JR, ed. *Reflux*

oesophagitis and the Angelchik prosthesis. New York: Elsevier, 1987: 59–84.
4. Stoddard CJ. Gastro-oesophageal reflux and management of reflux induced strictures. In: Taylor I, ed. *Progress in Surgery Vol. 2.* London: Churchill Livingstone, 1987: 46–67.
5. Angelchik JP, Cohen R. A new surgical procedure for the treatment of gastro-oesophageal reflux and hiatal hernia. *Surg Gynecol Obstet* 1979; **148**: 246–8.
6. Stuart RC, Dawson, K, Keeling P, Byrne PJ, Hennessey TPJ. A prospective randomised trial of Angelchik prosthesis *versus* Nissen fundoplication. *Br J Surg* 1989; **76**: 86–9.
7. Bland M. The design of experiments. In: Bland M, ed. *An Introduction to Medical Statistics.* Oxford: Oxford University Press, 1987: 6–29.
8. Wale RJ, Royston CMS, Bennett JR, Buckton GK. Prospective study of the Angelchik anti-reflux prosthesis. *Br J Surg* 1985; **72**: 520–4.
9. Morris DL, Jones J, Evans DF *et al.* Reflux versus dysphagia: an objective evaluation of the Angelchik prosthesis. *Br J Surg* 1985; **72**: 1017–20.
10. Gear MWL, Gillison EW, Dowling BL. Randomized prospective trial of the Angelchik anti-reflux prosthesis. *Br J Surg* 1984; **71**: 681–3.
11. Angelchik JP, Cohen R, Kravetz RE. A ten year appraisal of the anti-reflux prosthesis. *Am J Gastroenterol* 1983; **78**: 671–3.
12. Lilly MP, Slapsky SF, Thompson WR. Intraluminal erosion and migration of the Angelchik anti-reflux prosthesis. *Arch Surg* 1984; **119**: 849–53.
13. Mughal MM, Bancewicz J, Marples M. Oesophageal manometry and pH recording does not predict the bad results of Nissen fundoplication. *Br J Surg* 1990; **77**: 43–5.
14. Byar DP, Schoenfield DA, Green SB *et al.* Design considerations for AIDS trials. *N Engl J Med* 1990; **323**: 1343–8.
15. Pocock SJ, Hughes RP. Practical problems in interim analyses, with particular regard to estimation. *Controlled Clinical Trials* 1989; **10**: 209–15.

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Effective surgical treatment for mammary duct fistula

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Forty-two patients with 43 mammary duct fistulae, including 23 with a history of at least one previous unsuccessful operation, were treated by excision of the involved duct and fistula alone (15 fistulae) or excision of the fistula combined with total duct excision (28 fistulae). The wounds were closed primarily with antibiotic cover. Two patients had a minor wound infection which settled within 1 month of surgery; one patient developed superficial necrosis of the nipple and one patient required a second operation to excise a discharging sinus. No fistula recurrence has been identified after a median follow-up of 2·5 years. Excision of the involved duct and fistula alone, or excision of the fistula combined with total duct excision performed with antibiotic cover, is probably the treatment of choice for mammary duct fistula.

The term mammillary fistula was introduced by Atkins[1] to describe fistulae of lactiferous ducts, a condition originally described by Zuska and colleagues[2]. It is now more correctly called mammary duct fistula[3]. Treatment methods include laying open the fistula[1], excision and primary closure with or without antibiotic cover[4], and excision and secondary closure without antibiotic cover[4]. The present paper reviews a series of patients with mammary duct fistulae treated by fistula excision and primary closure with antibiotic cover.

Patients and methods

Forty-two patients aged 21–52 years (median age 36 years) with 43 mammary duct fistulae (one bilateral) had surgical excision of the fistula. The fistulae had been present for from 3 months to 22 years, 14 patients having had their fistula for more than 5 years (median length of symptoms 4 years). In 19 patients (20 fistulae) this was the first surgical procedure; 12 had undergone one previous operation, seven had undergone two operations, and four had undergone three or more operations. Eighteen fistulae were associated with complete inversion of the nipple and 24 were associated with nipple retraction at the site of the involved duct; the fistula in the remaining patient occurred following surgery to evert a partially retracted nipple.

While most fistulae followed excision and drainage of a non-lactating breast abscess ($n = 30$) or breast biopsy ($n = 9$), three arose from spontaneous discharge of an inflammatory mass and one followed previous surgery for an inverted nipple.

Forty of the fistulae had an external opening located at the areolar margin and three opened at the base of the nipple.

Treatment

All patients received intravenous antibiotics at the time of induction and at 8 and 16 h after surgery. Oral antibiotics were continued for 4 days. Fifteen patients were treated with 1 g cephradine and 500 mg metronidazole intravenously and 500 mg cephradine four times a day with 200 mg metronidazole three times a day orally. Twenty-seven patients were treated with amoxycillin and clavulanic acid given in a combined preparation in a dose of 1·2 g intravenously and 375 mg three times a day orally.

Operative procedure

The fistula was demonstrated with a lacrimal probe and, in the 40 fistulae with an external opening at the areolar margin, a circumareolar incision was made incorporating the exit site of the fistula. Two incisions, one incorporating the fistula exit site and a circumareolar incision, were utilized in the three patients with fistulae at the base of the nipple. The extent of the circumareolar incision in both groups was less than one-quarter of the circumference of the areola. The fistula was dissected underneath the areolar skin up to the back of the nipple, taking care to excise the involved duct completely up to and including a portion of nipple skin. If the nipple could be satisfactorily everted and this was the first operation for a mammary duct fistula, no other surgery was performed. In the 23 patients (23 fistulae) who had previously undergone unsuccessful operations for mammary duct fistula and in five further patients (five fistulae) where the nipple could not be everted after excision of the fistula alone, a total duct excision was performed and scar tissue deep to the nipple from previous operations was excised. Drains were not used after any operation and all nipples were left everted. Skin wounds were sutured with a subcuticular 4/0 Prolene® (Ethicon Ltd., Edinburgh, UK) or a 4/0 absorbable suture.

Patients were reviewed 10 days, 1 month and 3 months after surgery. Subsequent follow-up has been obtained for between 9 months and 5 years after surgery, with a median length of follow-up of 2·5 years. At 3 months all patients were asked whether there had been any change in nipple sensation following the most recent surgical procedure.

Results

Thirty-nine of the 43 wounds (in 38 patients) healed without infection or other complications. Two patients discharged a small amount of purulent material and were treated with a further 2-week course of oral amoxycillin and clavulanic acid combined. The infection settled within 1 month of surgery. One patient had superficial necrosis of the nipple. The tissues underneath were viable; the necrotic material had separated by 3 weeks and the nipple was fully healed by 4 weeks. One patient in whom this was the tenth operation over a 20-year period for mammary duct fistula developed a wound sinus. The sinus was found to pass down to the chest wall and was excised at a second operation. Although this patient has not had further trouble as a consequence of the multiple operations for mammary duct fistula, she has been left with marked breast asymmetry. During follow-up there have been no recurrences. Two patients complained of pain deep to the nipple in the immediate postoperative period which settled within 1 month of surgery, and two patients reported abnormal nipple sensation. Both patients had a history of seven and nine previous operations, respectively, and had multiple scars around their nipple. They did not think there had been a significant change in sensation after the most recent operation.

In all 43 fistulae, histological examination revealed evidence of active or previous periductal inflammation. Active periductal inflammation was seen principally in patients who were having their first operation for a fistula. In recurrent fistulae there was little or no evidence of ongoing inflammation but considerable periductal fibrosis, and this was considered to be a consequence of periductal inflammation rather than the result of previous operations. Significant duct dilatation was identified in the specimens of the four oldest patients.

Discussion

Mammary duct fistula is predominantly a complication of periductal mastitis[4]. The median age of presentation in this and

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other series is 36 years; the median age of patients with periductal mastitis is 32 years[4,5]. This 4-year difference is the same as the median length of symptoms in this series and may indicate that fistulae develop in the early stages of periductal mastitis. Bacteria, particularly anaerobic organisms, can be isolated from the lesions of periductal mastitis and mammary duct fistulae[6], explaining why simple excision of the fistula is associated with a significant infection and a high recurrence rate[4,7]. Excision of the fistula combined with appropriate antibiotic treatment may provide a cure even for fistulae refractory to previous surgical procedures. A combination of cephradine and metronidazole was felt to be the most appropriate antibiotic combination to cover organisms isolated from mammary duct fistulae[6]. Amoxycillin and clavulanic acid, which are now available as a combined preparation, can provide the same cover.

Complete excision of the fistula and affected duct can be performed cosmetically through a small circumareolar incision. Extension of the incision across the areola was not required and large amounts of tissue deep to the nipple were not usually excised, as advocated recently[8]. The fistula is usually very superficial and a likely cause of recurrence is dissection deep to the fistula tract. Primary suture of the wound can be performed after adequate haemostasis[8], although others prefer to leave the wound to heal by granulation[3].

In patients with recurrent fistulae the major breast ducts were excised in association with the fistula to ensure that other diseased ducts were removed and to allow correction of nipple inversion producing a better overall cosmetic result. The importance of complete removal of all the ducts and of correcting nipple inversion appears to be a major factor in ensuring that reoperations for this condition are successful[3]. Altered nipple sensation, which has been reported after major duct excision[9], was elicited in only two patients, both of whom had had several previous operations close to the nipple. This may be related to the smaller incisions used here compared with those used by others[9]. The only contraindication to total duct excision would be in women who wish to have more children and breastfeed.

All operations were performed by one surgeon in a specialized breast unit. All but two of the previous unsuccessful operations were performed in a general surgical unit without a major interest in breast disease. Neither of the two unsuccessful operations undertaken in specialist units was performed by a consultant surgeon. Mammary duct fistula is not a common problem[10] but can be associated with significant morbidity. These results and the experience in other centres[3] suggest that mammary duct fistula should be treated by surgeons with a specialist interest in the condition.

References

1. Atkins HJB. Mammillary fistula. *Br Med J* 1952; **ii**: 1473–4.
2. Zuska JJ, Crile F, Ayres WW. Fistulas of lactiferous ducts. *Am J Surg* 1951; **81**: 312–17.
3. Hughes LE. Non-lactational inflammation and duct ectasia. *Br Med Bull* 1991; **47**: 272–83.
4. Bundred NJ, Dixon JM, Chetty U, Forrest APM. Mammillary fistula. *Br J Surg* 1987; **74**: 466–8.
5. Dixon JM, Anderson TJ, Lumsden AB, Elton RA, Roberts MM Forrest APM. Mammary duct ectasia. *Br J Surg* 1983; **70**: 601–3.
6. Bundred NJ, Dixon JM, Lumsden AB *et al.* Are the lesions of duct ectasia sterile? *Br J Surg* 1985; **72**: 844–5.
7. Dixon JM, Chetty U, Forrest APM. Wound infections after breast biopsies. *Br J Surg* 1988; **75**: 918–19.
8. Rogers K. Breast abscesses and problems with lactation. In: Smallwood JA, Taylor I, eds. *Benign Breast Disease*. London: Arnold, 1990: 96–108.
9. Hadfield GJ. Noncosmetic operations for benign breast disease. *World J Surg* 1989; **13**: 757–60.
10. Lambert ME, Betts CD, Sellwood RA. Mammillary fistula. *Br J Surg* 1986; **73**: 367–8.

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Subareolar dissection for duct ectasia and periareolar sepsis

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Excision of the major duct system of the breast for symptoms owing to mammary duct ectasia may be curative, but recent reports have been less optimistic. A retrospective study (1978–1990) of 46 women (median age 38 years, range 18–78 years) who underwent subareolar dissection with antibiotic cover for symptoms associated with duct ectasia is presented. Thirty-three women presented without symptoms of overt sepsis (periareolar lump, nipple discharge or nipple retraction). Following subareolar dissection, six developed recurrent symptoms and five required further surgery. Thirteen women presented initially with abscesses. Eight abscesses recurred following incision and drainage, and one developed a mammillary fistula. Following subareolar dissection, six developed recurrent sepsis requiring further surgery.

Less than 6 per cent of all breast surgery is undertaken for the clinical syndrome of mammary duct ectasia[1,2]. However, this is associated with a significant morbidity and reoperation rate and represents a disproportionate workload for the surgeon and misery for the patient in whom the disease may run an intractable course.

Hadfield[3,4] reported that treatment by excision of the major duct system of the breast was curative. In 99 patients with duct ectasia, including 30 with periareolar sepsis, there was no recurrence of symptoms at 7 years follow-up. Similarly, Urban[5] reported on 113 patients with duct ectasia (including 19 with periareolar sepsis) treated in a similar manner, with no recurrence of symptoms at 14 years follow-up.

Recent reviews have shown that subareolar dissection may not be so effective, especially in the presence of periareolar sepsis. Thomas and colleagues[2] reported on 78 patients with mammary duct ectasia and found that, at 11 years follow-up, eight patients had required further surgery after subareolar dissection. Seven of these had presented with periareolar sepsis. Browning and colleagues[1] showed good results in the treatment of mammary duct ectasia associated with nipple change, but for those symptoms associated with sepsis the reoperation rate was 44 per cent. Hughes[6] reported on 122 patients treated by subareolar dissection over 10 years and found that 28 per cent developed further problems, especially if the indication for surgery was breast disease related to duct ectasia.

This paper reports a retrospective review of subareolar dissection for the treatment of symptoms owing to mammary duct ectasia from 1978 to 1990.

Patients and methods

All patients were operated on by a single operator (E.A.B.). The technique of subareolar dissection is described in *Figure 1*.

Antibiotics (oral erythromycin and metronidazole) were started with the premedication and continued for 5 days after operation to cover the expected range of organisms associated with the lesions of mammary duct ectasia[7]. The definitive operation was only performed once the original sepsis was quiescent after treatment with antibiotics or surgical drainage. In all patients the histological diagnosis of duct ectasia was confirmed histologically.

A total of 54 women underwent subareolar dissection. Eight were lost to follow-up. The median age of the remaining 46 women was 38 years (range 18–78 years). The median length of follow-up was 1 year (range 3 months to 12 years).

Symptoms at presentation are shown in *Table 1*.

Results

Of the 33 women undergoing subareolar dissection for symptoms not associated with sepsis, six developed recurrent

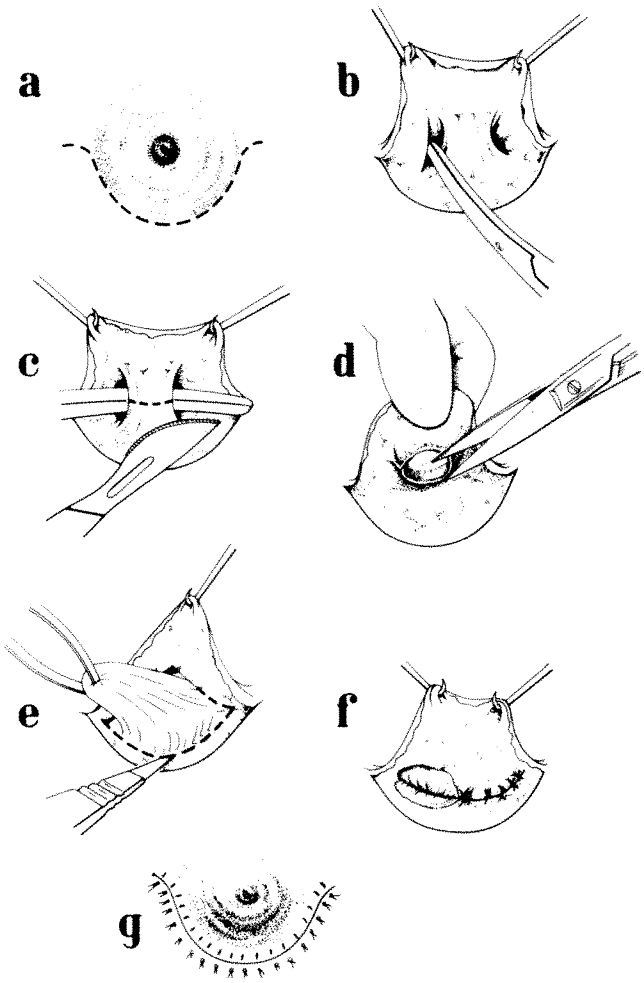

Figure 1 *Technique of subareolar dissection.* **a** *Circumareolar incision usually curved below the areola;* **b** *elevation of nipple areolar complex by sharp scissor dissection;* **c** *separation of all major ducts from the base of the nipple by passing a curved haemostat around the nipple base and dividing with a knife;* **d** *the nipple base is then carefully pared down to remove all ductal tissue. Care is taken to avoid devascularization of the nipple skin. A purse-string suture of catgut is inserted through the nipple base to hold it everted without causing nipple necrosis;* **e** *the central duct system is then cored out of the middle of the breast disc;* **f** *after haemostasis, the cavity is closed in layers of interrupted catgut without the use of a drain;* **g** *the areolar skin is sutured back into position with interrupted non-absorbable sutures*

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Table 1 *Symptoms at presentation*

	No. of patients
Periareolar lump	12
Nipple discharge	8
Nipple retraction	6
Nipple discharge and retraction	7
Periareolar sepsis	13

symptoms. These were periareolar lump (two), nipple discharge (one), nipple retraction (one) and nipple retraction and discharge (two). The patient with nipple discharge did not require further surgery as this settled spontaneously. The remaining five women required further subareolar exploration and dissection for relief of symptoms.

All 13 women with symptoms associated with sepsis presented initially with non-lactational periareolar abscesses. In five patients the abscesses settled with antibiotic treatment or by spontaneous discharge before definitive subareolar dissection. Eight patients developed recurrent abscesses which required incision and drainage, and one of these developed a mammillary fistula before subareolar dissection. Of these 13 women, six developed recurrent symptoms and all required further surgery. Two patients developed periareolar inflammation which failed to settle on prolonged antibiotic treatment and required further subareolar dissection. Two patients developed recurrent abscesses requiring incision and drainage before repeat subareolar dissection. One patient developed a mammillary fistula which required laying open and packing. One patient required no less than six incision and drainage procedures for abscesses occurring in both breasts, and eventually accepted bilateral mastectomies.

Discussion

These results contrast with the early reports by Hadfield and Urban[3-5] describing the success of subareolar dissection as a curative operation, and agree with more recent reports indicating a disappointing result[1,2,6]. A number of reasons for failure of the operation have been suggested. Inadequate removal of major ductal tissue, either from the nipple base or breast disc, and failure to evert the nipple lead to recurrent symptoms[6].

The technique varies from that originally described by Hadfield and Urban in two ways, these being the use of antibiotics and drains for at least 24 h. Drains were not used in this series since overt sepsis was a contraindication to a definitive operation; a collection of pus was incised and drained before subareolar dissection. Suction drainage was avoided as this promotes a concavity in the breast disc with nipple reinversion. Primary closure was part of the surgical technique to obliterate the dead space. Perioperative antibiotic cover was used in all cases. It is recognized that bacteria are found in the lesions of duct ectasia, even in the absence of overt sepsis[7]. The treatment of lactational breast abscesses, however, by incision and primary suture with antibiotic cover has achieved good results[8]. It would seem that the difficulty in eradicating sepsis is related to the underlying pathology of mammary duct ectasia.

These results demonstrate that subareolar dissection with antibiotic cover does not invariably provide a cure, and nearly half of those patients presenting with periareolar sepsis will eventually require further surgery. Initial treatment for these patients should be more conservative.

Periareolar inflammation may be treated successfully with antibiotics, avoiding surgical intervention[9]. The development of periareolar pus, however, requires surgical drainage by laying open and loosely packing the cavity, and allowing the wound to granulate[10]. This may result in a mammillary fistula which should eventually be treated by excision of the involved duct and fistula with primary suture under antibiotic cover. Ultimately, intractable periareolar sepsis may require formal subareolar dissection with appropriate antibiotic cover, paying particular attention to the points of detail in *Figure 1*. Patients undergoing surgery should be warned of the risk of recurrent problems and the possible loss of nipple sensation. Nipple necrosis is an uncommon complication following repeated surgery. In the absence of a precise understanding of the aetiology of mammary duct ectasia, treatment of its complications remains empirical and controversial.

References

1. Browning J, Bigrigg A, Taylor I. Symptomatic and incidental mammary duct ectasia. *J R Soc Med* 1986; **79**: 715–16.
2. Thomas W, Williamson R, Davies J, Webb A. The clinical syndrome of mammary duct ectasia. *Br J Surg* 1982; **69**: 423–5.
3. Hadfield J. Excision of the major duct system for benign disease of the breast. *Br J Surg* 1960; **47**: 472–7.
4. Hadfield J. Further experience of the operation for excision of the major duct system of the breast. *Br J Surg* 1968; **55**: 530–5.
5. Urban J. Excision of the major duct system of the breast. *Cancer* 1963; **16**: 516–20.
6. Hughes L. Management of recurrent infection following surgery for periductal mastitis. *Br J Clin Pract* 1989; **43**(Suppl 68): 81–5.
7. Bundred N, Dixon J, Lumsden A *et al.* Are the lesions of duct ectasia sterile? *Br J Surg* 1985; **72**: 844–5.
8. Benson E, Goodman M. Incision with primary suture in the treatment of acute puerperal breast abscess. *Br J Surg* 1970; **57**: 55–8.
9. Dixon J, Lee E, Greenall M. Treatment of periareolar inflammation associated with periductal mastitis using metronidazole and flucloxacillin: a preliminary report. *Br J Clin Pract* 1988; **42**: 78–80.
10. Benson E. The management of breast abscesses. *Curr Pract Surg* 1991; **3**: 108–12.

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Seeding of human microvascular endothelial cells onto polytetrafluoroethylene graft material

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Microvascular endothelial cells from human omental samples were isolated and grown. Adhesion to polytetrafluoroethylene vascular graft material was then studied using scanning electron microscopy and adhesion of cells labelled with indium-111. Grafts coated with fibronectin and type I collagen were found to promote the best adhesion of cells at times up to 90 min. A coating of blood clot matrix was less effective but still resulted in a threefold increase in cell adhesion compared with controls.

Prosthetic vascular grafts are increasingly being used to save patients from severe limb pain or amputation. However, distal prosthetic vascular grafts in humans are known to have a higher failure rate than bypasses performed using autologous vein, even after an interval of several years[1]. Two major reasons for this have been suggested: firstly, the lack of compliance in prosthetic grafts[2], and secondly the fact that in humans such grafts fail to develop an endothelial lining[3]. The belief that the endothelium is the important factor has prompted work on the seeding of endothelial cells onto the surface of prosthetic graft materials in an attempt to make the artificial graft behave more like a native vessel[4]. Such work in animals has shown clear advantage from seeding[5–8].

One major problem in transferring this experimental success to a clinical trial has been to find a source of endothelial cells that could be easily and rapidly harvested in numbers large enough to allow immediate high-density vascular graft seeding. Human subcutaneous fat and omentum have been proposed as such a source[9–13]. In this study human omental microvascular endothelial cells (HOTMECs) have been isolated, and their ability to adhere to polytetrafluoroethylene (PTFE) graft material, treated in different ways, has been studied.

Materials and methods

Harvest of human omental microvascular endothelial cells

A modification of the method of Kern *et al.*[9] was used to prepare HOTMECs for culture. Omental fat (20–75 g) was obtained from patients undergoing routine abdominal surgery. Fully informed consent was obtained in all cases and the study was approved by the hospital's ethical committee. The fat was collected into warm phosphate buffered saline (PBS) and finely minced before incubation with a collagenase solution (Boehringer-Mannheim Corporation, Lewes, UK), at a concentration of 1 g/100 ml in PBS, for 30 min at 37°C. The digest was then filtered through a 250 μm mesh to remove debris and the collagenase was neutralized with M199 medium (Gibco BRL, Uxbridge, UK) containing 20 per cent fetal calf serum (FCS) (Sigma, Poole, UK). The slurry was then allowed to settle for 5 min, during which time the adipocytes formed a separate layer at the surface, which was removed by aspiration. The remaining solution, rich in vessel fragments, was spun at 20 000 r.p.m. in 45 per cent Percoll (Pharmacia, Milton Keynes, UK) in M199 medium at 20°C for 20 min. At the end of this time the microvessel fragments had formed a layer near the top of the density gradient with the red cells and single cells further down. This endothelial cell-rich layer was removed and placed into culture in M199 medium containing 20 per cent FCS. Cells were characterized as endothelial by their cobblestone monolayer appearance in culture, by the uptake of diacetylated low-density lipoprotein (Biogenesis, Bournemouth, UK) and by positive immunofluorescent staining for von Willebrand's factor. For seeding experiments, confluent cultures at first passage were detached using trypsin–ethylenediaminetetra-acetic acid (EDTA).

Graft preparation

Discs of PTFE graft material of 0·5 cm^2 area (W. L. Gore and Associates Incorporated, Arizona, USA) were immobilized in modified Eppendorf tubes according to the method of Budd *et al.*[14]. As well as control (untreated) segments, the following surface treatments were studied:

1. Fibronectin (Sigma) solution at a concentration of 18 μg/cm^2 was added to each well and allowed to dry in air overnight.
2. Collagen type I (Sigma) at a concentration of 10 μg/cm^2 in acetic acid was added to each well and allowed to dry in air overnight. Wells were then washed twice with warm culture medium before cells were added.
3. Gelatin (Sigma), 100 μl 0·1 per cent solution, was added to each well and allowed to dry in air overnight.
4. Polylysine (Sigma) was added at a concentration of 0·002 mg/cm^2 and allowed to dry in air overnight. Wells were then washed twice before cells were added.
5. Heparinized plasma was added to each well and left for 1 h before washing with warm culture medium.
6. Fresh (unheparinized) blood was added to each graft well and allowed to clot. This was left undisturbed for 1 h before being washed away with warm culture medium.

Visual assessment by scanning electron microscopy

Graft segments were prepared as above, i.e. controls and grafts treated with fibronectin, collagen, gelatin, polylysine, heparinized plasma and blood clot. Confluent cultures of HOTMECs were detached using trypsin–EDTA and the trypsin was neutralized with serum-containing medium. After washing and resuspending in fresh medium, supraconfluent numbers of microvascular endothelial cells ($> 2{\cdot}5 \times 10^5$) were added to each graft well for 1 h before fixation in 3 per cent glutaraldehyde in cacodylate buffer. The graft segments were then assessed by scanning electron microscopy.

Indium labelling experiments

The method of Sharefkin *et al.* was used[15]. Confluent cultures were detached using trypsin–EDTA and the cells were suspended in 1 ml serum-free medium; 100 μCi indium-111 oxine (Amersham International, Little Chalfont, UK) was added and the suspension was incubated for 15 min at 37°C. The cells were then washed three times with medium containing 20 per cent FCS and were finally resuspended in 5 ml of medium containing 20 per cent FCS before seeding. The washings were kept for cell counting and assessment of labelling efficiency. Cell viability, as assessed by trypan blue exclusion, was always greater than 95 per cent. Mean(s.d.) labelling efficiency was 81·8(4·3) per cent and mean(s.d.) number of cells seeded per well was $6{\cdot}5 \times 10^4(1{\cdot}1 \times 10^4)$.

Indium-labelled cell suspension (100 μl) was then added to each of the graft wells, and the wells were incubated at 37°C in air. At 10, 30, 60 and 90 min, graft wells were washed twice with fresh warm medium. Both graft segments and washings were kept for subsequent measurement of indium-111 by counting in a gamma well counter.

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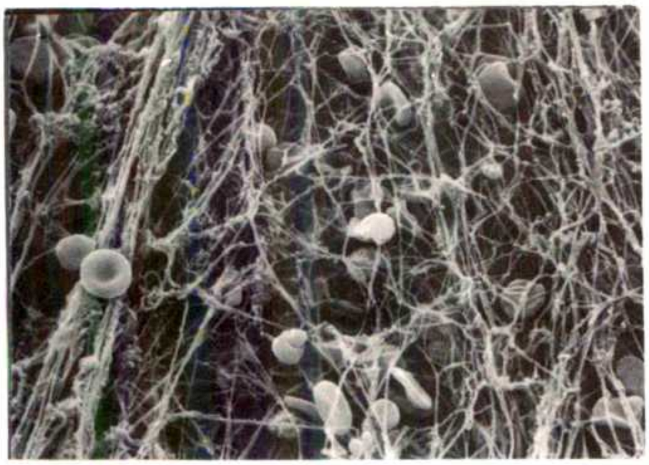

Figure 1 *Scanning electron micrograph (original magnification × 2050) showing polytetrafluoroethylene covered with a fibrin meshwork, containing some trapped red blood cells, after incubation with whole blood for 1 h*

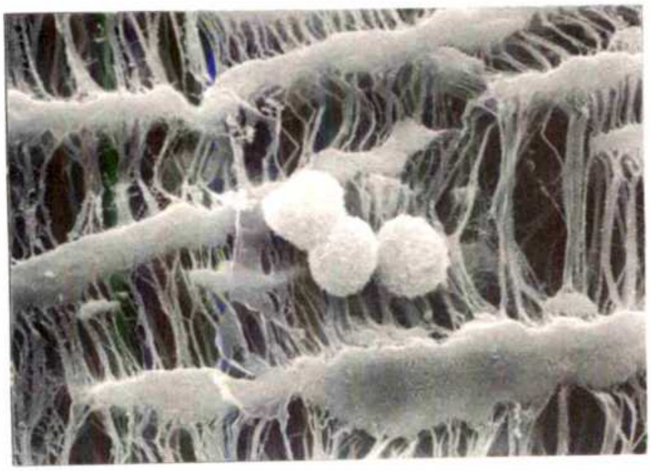

Figure 2 *Scanning electron micrograph (original magnification × 2050) of uncoated polytetrafluoroethylene after incubation with human omental microvascular endothelial cells for 1 h. Few cells are attached and none is flattening or spreading*

Calculation of results

Percentage cell attachment was calculated using the following formula:

$$\% \text{ Cell attachment} = \frac{\text{Counts on graft}}{\text{Counts in washings} + \text{counts on graft}} \times 100$$

Five repetitions of the experiment were performed, using cells from a different patient on each occasion. Statistical analysis was performed using the Mann–Whitney *U* test.

Results

Visual assessment of cell attachment

Treatment of PTFE segments with whole blood for 1 h was found to produce a uniform fibrin coating to the graft (*Figure 1*). Heparinized plasma produced no such surface coating after 1 h.

On control graft segments, few cells were found to be attached after 1 h, and those that were attached were rounded and not spreading (*Figure 2*). Surfaces treated with gelatin, polylysine and plasma produced results similar to those obtained with control grafts, with few cells attached. In contrast, grafts treated with blood clot, collagen and fibronectin showed increased numbers of attached cells, which were flattened and becoming confluent. In particular, on the fibronectin-coated grafts, there was almost a complete monolayer formed after 1 h (*Figure 3*). Grafts treated with collagen and blood clot produced a more patchy appearance (*Figure 4*), but again cells were seen flattening and attaching after 1 h. Cells did not exhibit the surface microvilli said to be typical of mesothelium[16].

Indium labelling experiments

On the basis of the results of the pilot experiment controls, PTFE graft surfaces treated with collagen, fibronectin and blood clot were further evaluated using cells labelled with indium-111 oxine. The results, expressed as percentage cell attachment over 90 min, are shown in *Figure 5*.

All the treatments produced statistically better adhesion at all times from 10 min onwards compared with control PTFE surfaces ($P<0.01$). Of the treatments, fibronectin was found to produce the best cell adherence (60 per cent at 90 min) compared with collagen (46 per cent), blood clot (34 per cent) and controls (11 per cent). These differences were statistically significant ($P<0.05$), as were differences at 30 and 60 min ($P<0.05$).

With all three treatments studied, >70 per cent of the cells adherent by 90 min were adherent by 30 min, indicating that initial adherence is rapid.

Discussion

Despite the advantages of endothelial seeding of synthetic grafts demonstrated in animal studies[5–8], there has been no widespread introduction of seeding into clinical practice[4]. This

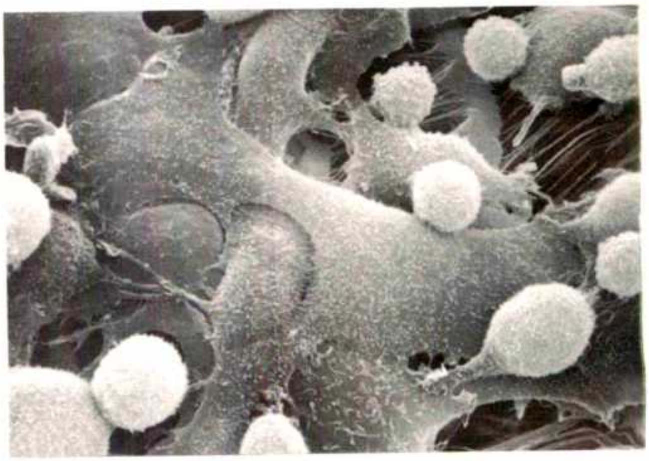

Figure 3 *Scanning electron micrograph (original magnification × 2050) of fibronectin-coated polytetrafluoroethylene after incubation with human omental microvascular endothelial cells for 1 h. Many cells have attached and are seen flattening and spreading*

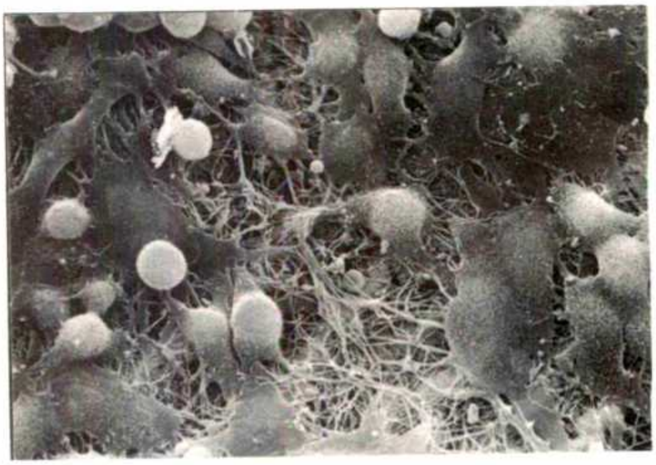

Figure 4 *Scanning electron micrograph (original magnification × 1050) of blood clot-treated polytetrafluoroethylene after incubation with human omental microvascular endothelial cells for 1 h. Many cells have attached and are seen flattening and spreading*

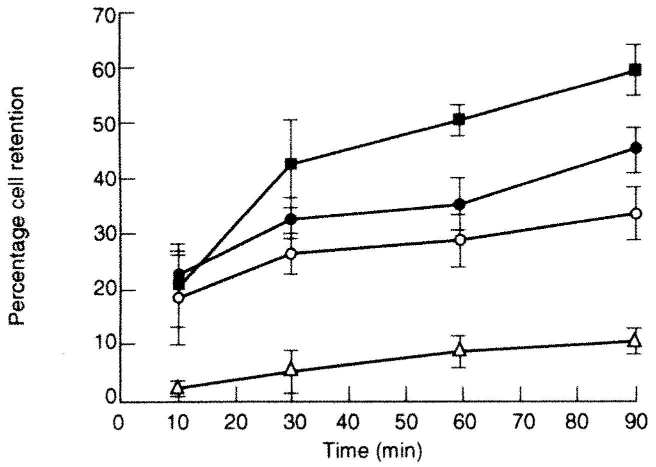

Figure 5 *Graph showing percentage cell retention against time for untreated polytetrafluoroethylene (PTFE) (control) and PTFE treated with fibronectin, collagen and blood clot. Data points represent the mean of five experiments and the error bars represent s.d.* ■, *Fibronectin;* ●, *collagen;* ○, *blood;* △, *control*

is due in part to lack of a suitable source of endothelial cells for human seeding. Other problems include the difficulties of remote assessment of grafts after implantation and contamination of cell yields with fibroblasts and smooth muscle cells. Trials in humans have, to date, produced only equivocal results[17–23].

The use of microvascular endothelium derived from human omental fat was investigated in the hope that it might prove a useful source of cells for seeding vascular grafts. This source has the potential to provide a large number of endothelial cells, allowing immediate high-density graft seeding[12,24–26]. In our hands the technique yields up to $1\cdot5 \times 10^5$ cells/g omentum although Jarrell's group[13] have reported yields of $1\cdot25 \times 10^6$ cells/g.

There has been debate about the true endothelial nature of these cells, some workers suggesting that they might be mesothelial[16,27–29]. However, they have been shown to produce prostacyclin in similar quantities to large vessel endothelium and by similar mechanisms[30], as well as to stain positively for von Willebrand factor and to take up diacetylated low-density lipoprotein[29], both of which are features of true endothelium. In addition, they are known to produce tissue plasminogen activator in greater quantities than human umbilical vein endothelial cells[31,32]. They do, therefore, possess the physiological properties which make them attractive as a cell source for producing a non-thrombogenic lining to a vascular prosthesis. Perhaps the debate as to their true origin is academic, since mesothelium has independently been proposed as a suitable cell source for vascular graft seeding[33,34].

Currently, PTFE is the prosthetic material most often used for vascular bypass below the inguinal ligament and as such it would be the most attractive choice for endothelial cell seeding trials. Unfortunately, endothelial cells adhere relatively poorly to untreated PTFE[35,36]. We chose to investigate gelatin and polylysine coating because these are substances used to promote endothelial cell adhesion to tissue culture flasks. However, they appeared to offer no advantage over untreated control PTFE under the conditions studied. In contrast, fibronectin, collagen and blood clot treatment all resulted in significantly increased cell adhesion compared with control PTFE.

These results are similar to those reported by other groups using large vessel endothelium for seeding[14,35,37–40]. Of the treatments studied, fibronectin promoted the best attachment, as might be expected of a substance which is a component of normal basement membrane. There are, however, potential disadvantages in using fibronectin. It is expensive and requires that the graft be coated before surgery. In addition, as a blood-derived product, there is at least the theoretical risk of transmission of viral agents such as the hepatitis viruses and the human immunodeficiency virus. Collagen as a coating is much cheaper than fibronectin and is also a component of basement membrane, but again it has the disadvantage of requiring pretreatment of the graft. Furthermore, both fibronectin and collagen coating of a graft may result in an initial increase in graft thrombogenicity[41], which may pose clinical difficulties.

Blood clot matrix has been suggested as a suitable surface for endothelial cell seeding[42]. This treatment is potentially the most applicable to vascular surgical practice, from the specialist centre to the district general hospital, and can be performed within the time-course of a normal vascular procedure. Unlike Vohra *et al.*[42], who used saphenous vein endothelial cells and studied the effects of surface coatings in a flow model, we did not find that blood clot matrix performed better than fibronectin. However, the disadvantages of lower initial cell adhesion may be overcome by using a source of cells, such as HOTMECs, which allows initial supraconfluent seeding.

With appropriate surface modification, microvascular endothelium derived from human omentum will adhere to PTFE vascular graft material. Fibronectin and collagen promote the best adhesion, but there may be disadvantages in the use of both substances. Pretreatment with blood clot is a viable alternative, which has the advantages of low cost, requiring no preparation of the graft before the vascular procedure, and causing no increase in early thrombogenicity. Further work is needed to investigate whether seeded cells remain attached after graft implantation and exposure to the shear forces found in flowing blood.

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References

1. Michaels JA. Choice of material for above-knee femoropopliteal bypass graft. *Br J Surg* 1989; **76**: 7–14.
2. Schmitz-Rixen T, Hamilton G. Compliance: a critical parameter for maintenance of arterial reconstruction: In: Greenhalgh RM, Hollier LH, eds. *The Maintenance of Arterial Reconstruction.* London: Saunders, 1991: 23–43.
3. Berger K, Sauvage LR, Rao AM, Wood SJ. Healing of arterial prosthesis in man: its incompleteness. *Ann Surg* 1972; **175**: 118–27.
4. Callow AD. Endothelial cell seeding: problems and expectations. *J Vasc Surg* 1987; **6**: 318–19.
5. Stanley JC, Burkel WM, Graham LM, Lindblad B. Endothelial cell seeding of synthetic vascular prostheses. *Acta Chir Scand* 1985; **529**: 17–28.
6. Douville EC, Kempczinski RF, Birinyi LK, Ramalanjaona G. Impact of endothelial cell seeding on long-term patency and subendothelial proliferation in a small-caliber highly porous polytetrafluoroethylene graft. *J Vasc Surg* 1987; **5**: 544–50.
7. Sharefkin JB, Latker C, Smith M, Cruess D, Clagett P, Rich NM. Early normalization of platelet survival by endothelial seeding of Dacron arterial prostheses in dogs. *Surgery* 1982; **92**: 385–93.
8. Schneider PA, Hanson SR, Price TM, Harker LA. Preformed confluent endothelial cell monolayers prevent early platelet deposition on vascular prostheses in baboons. *J Vasc Surg* 1988; **8**: 229–35.
9. Kern PA, Knedler A, Eckel RH. Isolation and culture of microvascular endothelium from human adipose tissue. *J Clin Invest* 1983; **71**: 1822–9.
10. Williams SK, Jarrell BE, Rose DG. Isolation of human fat derived microvessel endothelial cells for use in vascular graft endothelialisation. In: Zilla PP, Fasol RD, Deutsch M, eds. *Endothelialization of Vascular Grafts.* Basel: Karger, 1987: 211–17.
11. Pearce WH, Rutherford RB, Whitehill TA *et al.* Successful endothelial seeding with omentally derived microvascular endothelial cells. *J Vasc Surg* 1987; **5**: 203–10.
12. Jarrell BE, Williams SK, Stokes G *et al.* Use of freshly isolated

capillary endothelial cells for the immediate establishment of a monolayer on a vascular graft at surgery. *Surgery* 1986; **100**: 392–9.

13. Rupnick MA, Hubbard FA, Pratt K, Jarrell BE, Williams SK. Endothelialization of vascular prosthetic surfaces after seeding or sodding with human microvascular endothelial cells. *J Vasc Surg* 1989; **6**: 788–95.
14. Budd JS, Bell PRF, James RF. Attachment of indium-111 labelled endothelial cells to pretreated polytetrafluoroethylene vascular grafts. *Br J Surg* 1989; **76**: 1259–61.
15. Sharefkin JB, Lather C, Smith M, Rich NM. Endothelial cell labeling with indium-111 oxine as a marker of cell attachment to bioprosthetic surfaces. *J Biomed Mat Res* 1983; **17**: 345–57.
16. Visser MJT, van Bockel JH, van Muijen GNP, van Hinsbergh VWM. Cells derived from omental fat tissue and used for seeding vascular prostheses are not endothelial in origin. *J Vasc Surg* 1991; **13**: 373–81.
17. Herring M, Gardner A, Glover J. Seeding human arterial prostheses with mechanically derived endothelium: the detrimental effect of smoking. *J Vasc Surg* 1984; **1**: 279–89.
18. Herring M, Compton RS, LeGrand D, Gardner AL, Madison DL, Glover JL. Endothelial seeding of polytetrafluoroethylene popliteal bypasses. *J Vasc Surg* 1987; **6**: 114–18.
19. Ortenwall P, Wadenvik H, Kutti J, Risberg B. Endothelial cell seeding reduces thrombogenicity of Dacron grafts in humans. *J Vasc Surg* 1990; **11**: 403–10.
20. Ortenwall P, Wadenvik H, Risberg B. Reduced platelet deposition on seeded *versus* unseeded segments of expanded polytetrafluoroethylene grafts: clinical observations after a 6-month follow-up. *J Vasc Surg* 1989; **10**: 374–80.
21. Fasol R, Zilla P, Deutsch M, Grimm M, Fischlein T, Laufer G. Human endothelial cell seeding: evaluation of its effectiveness by platelet parameters after one year. *J Vasc Surg* 1989; **9**: 432–6.
22. Walker MG, Thomson GJL, Shaw JW. Endothelial cell seeded *versus* non-seeded grafts in patients with severe peripheral vascular disease: preliminary results. In: Zilla PP, Fasol RD, Deutsch RD, eds. *Endothelialization of Vascular Grafts*. Basel: Karger, 1987: 245–8.
23. Meerbaum SO, Sharp WV, Schmidt SP. Lower extremity revascularisation with PTFE grafts seeded with microvascular endothelial cells. *International Society for Applied Cardiovascular Biology*. 1990 (Abstract).
24. Jarrell BE, Williams SK, Carabasi RA, Hubbard FA. Immediate vascular graft monolayers using microvessel endothelial cells. In: Herring M, Glover J, eds. *Endothelial Seeding in Vascular Surgery*. New York: Grune and Stratton, 1987: 37–55.
25. Sharp WV, Schmidt SP, Meerbaum SO, Pippert TR. Derivation of human microvascular endothelial cells for prosthetic vascular graft seeding. *Ann Vasc Surg* 1989; **3**: 104–7.
26. Sterpetti AV, Hunter WJ, Schultz RD *et al.* Seeding with endothelial cells derived from the microvessels of the omentum and from the jugular vein: a comparative study. *J Vasc Surg* 1988; **7**: 677–84.
27. Takahashi K, Sawasaki Y, Goto T, Hata J, Mukai K. Cobblestone monolayer cells from human omental adipose tissue are possibly mesothelial, not endothelial. *In Vitro Cell Dev Biol* 1989; **25**: 109–11.
28. van Hinsbergh VW, Kooistra T, Scheffer MA, van Bockel JH, van Muijen GN. Characterization and fibrinolytic properties of human omental tissue mesothelial cells: comparison with endothelial cells. *Blood* 1990; **75**: 1490–7.
29. Stansby G, Shukla N, Fuller B, Hamilton G. Characterisation of microvascular endothelial cells derived from human fat. *Biochem Soc Trans* 1991; **19**(Suppl): 168.
30. Stansby G, Shukla N, Hamilton G, Jeremy J. Comparison of prostanoid synthesis in cultured human vascular endothelial cells derived from omentum and umbilical vein. *Eur J Vasc Surg* 1991; **5**: 501–6.
31. Speiser W, Anders E, Binder BR, Muller-Berghaus G. Clot lysis mediated by cultured human microvascular endothelial cells. *Thromb Haemost* 1988; **60**: 463–7.
32. Speiser W, Anders E, Preissner KT, Wagner O, Muller-Berghaus G. Differences in coagulant and fibrinolytic activities of cultured human endothelial cells derived from omental tissue microvessels and umbilical veins. *Blood* 1987; **3**: 964–7.
33. Bull HA, Pittilo RM, Drury J *et al.* Effects of autologous mesothelial cell seeding on prostacyclin production within Dacron arterial prostheses. *Br J Surg* 1988; **75**: 671–4.
34. Clarke JMF, Pittilo RM, Nicholson LJ, Woolf N, Marston A. Seeding Dacron arterial prostheses with peritoneal mesothelial cells: a preliminary morphological study. *Br J Surg* 1984; **71**: 492–4.
35. Seeger JM, Klingman N. Improved endothelial cell seeding with cultured cells and fibronectin-coated grafts. *J Surg Res* 1985; **38**: 641–7.
36. Rosenman JE, Kempczinski RF, Pearce WH, Silberstein EB. Kinetics of endothelial cell seeding. *J Vasc Surg* 1985; **2**: 778–84.
37. Ramalanjaona G, Kempczinski RF, Rosenman JE, Douville EC, Silberstein EB. The effect of fibronectin coating on endothelial cell kinetics in polytetrafluoroethylene grafts. *J Vasc Surg* 1986; **3**: 264–72.
38. Kesler KA, Herring M, Arnold MP *et al.* Enhanced strength of endothelial cell attachment on polyester elastomer and polytetrafluoroethylene graft surfaces with fibronectin substrate. *J Vasc Surg* 1986; **3**: 58–64.
39. Kaehler J, Zilla P, Fasol R, Deutsch M, Kadletz M. Precoating substrate and surface configuration determine adherence and spreading of seeded endothelial cells on polytetrafluoroethylene grafts. *J Vasc Surg* 1989; **9**: 535–41.
40. Seeger JM, Klingman N. Improved *in vivo* endothelialization of prosthetic grafts by surface modification with fibronectin. *J Vasc Surg* 1988; **8**: 476–82.
41. Kempczinski RF, Ramalanjaona GR, Douville C, Silberstein EB. Thrombogenicity of a fibronectin-coated, experimental polytetrafluoroethylene graft. *Surgery* 1987; **101**: 439–44.
42. Vohra RK, Thomson GJL, Sharma H, Carr HMH, Walker MG. Effects of shear stress on endothelial cell monolayers on expanded polytetrafluoroethylene (ePTFE) grafts using preclot and fibronectin matrices. *Eur J Vasc Surg* 1990; **4**: 33–41.

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Surgical management of the thoracic outlet compression syndrome

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There is some disagreement about whether the first rib should be excised in the presence of a cervical rib for the relief of the thoracic outlet compression syndrome (TOCS). Over a 14-year period (1975–1988) 58 patients have undergone surgery for TOCS. Forty-four patients (76 per cent) had vascular symptoms, 28 (48 per cent) with a neurological component; 11 (19 per cent) had only neurological symptoms. Thirty-six patients (62 per cent) had the first rib excised; 19 (33 per cent) had a cervical rib excised; two (3 per cent) had a division of fibrous bands; and one patient had a large transverse process resected. Follow-up details were available on 53 patients (91 per cent). Overall 38 (72 per cent) were cured of their symptoms, 11 (21 per cent) had a significant improvement, and four (8 per cent) showed no improvement. There was no significant difference between the results following excision of a cervical rib or of a first rib in terms of relief of symptoms. In patients with TOCS who have a cervical rib, excision of the cervical rib alone without excision of the first rib would appear to be an appropriate treatment.

Thoracic outlet compression syndrome (TOCS) presents with symptoms resulting from pressure on either the subclavian vessels or the lower trunk of the brachial plexus. The surgical relief of TOCS by excision of a cervical rib was first described in 1861[1] and subsequently by excision of the first rib in 1903[2]. Controversy exists as to which of these is the more beneficial in the treatment of symptoms in the presence of a cervical rib[3–5]. This paper describes an experience of treating 58 patients (66 limbs) with TOCS.

Patients and methods

Over a 14-year period 58 patients (40 females and 18 males) with a mean age of 33 years (range 15–58 years) have been operated on for TOCS. The data were collected prospectively before review. The symptoms at the time of presentation have been divided into arterial, Raynaud's, neurological, arterial/neurological, venous and others. The presence or absence of a cervical rib and the type of operative procedure performed were noted. The policy was to perform only a cervical rib excision in the presence of a cervical rib and not to combine it with a first rib excision. Angiography, venography and neurophysiological tests were performed in patients when clinically indicated.

The outcome has been assessed at a minimum of 2 years by dividing the results into three groups: those patients who are cured, those who have had partial improvement, and those who have had no improvement of symptoms. Any resultant complications of the operation were documented.

Results

Of the 58 patients presenting with TOCS, 22 had cervical ribs (14 bilateral). The nature of the presenting symptoms is shown in *Table 1*. Forty-four patients (76 per cent) had vascular symptoms, 41 secondary to compression and three from Raynaud's syndrome. Twenty-eight patients (48 per cent) had a neurological component; neurological compression alone was implicated in 11 patients; and a combination of arterial and neurological symptoms occurred in 17 patients. Venous symptoms alone occurred in 12 patients (21 per cent).

Eight patients (14 per cent) had bilateral symptoms (all three patients with Raynaud's, two with venous symptoms and three in the arterial/neurological group) which required surgery. The nature of the symptoms necessitating bilateral surgery in a patient was the same for each limb. Forty-seven patients (81 per cent) had angiography, 11 (19 per cent) had venography before operation and 12 (21 per cent) had neurophysiological tests. No patient received treatment for an asymptomatic cervical rib.

Thirty-six patients (62 per cent) had the first rib excised (four bilateral); two of these patients had had previous cervical rib surgery. Nineteen patients (33 per cent) underwent cervical rib excision alone (four bilateral); two patients (3 per cent) underwent division of fibrous bands; and one patient had a resection of a transverse process. In total, surgery was performed for symptoms in 66 limbs, always via a supraclavicular approach. Two patients required arterial thrombectomy and two patients underwent prestellate sympathectomy.

Follow-up data were available for 53 patients (91 per cent) and the outcome in terms of relief of symptoms is shown in

Table 1 *Nature of the presenting symptoms in 58 patients with and without a cervical rib*

Symptoms	No. of patients
Presence of a cervical rib	
Arterial	5
Raynaud's	1
Arterial/neurological	8
Neurological	6
Venous	2
Total	22
Absence of a cervical rib	
Arterial	7
Raynaud's	2
Arterial/neurological	9
Neurological	5
Venous	10
Other	3
Total	36

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Table 2 *Symptomatic outcome of surgery in 21 patients with a cervical rib and in 32 without*

	Total no. of patients	Cure	Improvement	No improvement
Presence of a cervical rib				
Arterial	5*	4	1	
Raynaud's	1		1	
Arterial/ neurological	8	8		
Neurological	5	5†		
Venous	2	2		
Total	21	19	2	0
Absence of a cervical rib				
Arterial	6	3	2‡	1
Raynaud's	2		2	
Arterial/ neurological	7	6		1
Neurological	5	3		2
Venous	9	5	4	
Other	3	2	1	
Total	32	19	9	4

*One patient had fibrous bands divided; †two patients had first rib excision; ‡one patient had fibrous bands divided and the other had a transverse process removed

Table 3 *Complications after surgery*

Complication	Number
Wound complication	2 (1 haematoma, 1 keloid)
Pneumothorax	2
Haemothorax	1
Numbness	3

Table 2. In this group of patients, 38 (72 per cent) were cured, 11 (21 per cent) were improved and four (8 per cent) were not improved. In terms of limbs ($n = 61$), 45 (74 per cent) were cured. Full details were available in 35 patients with vascular compression. All 15 patients who underwent cervical rib excision alone showed improvement whereas 18 patients (90 per cent) who underwent first rib excision showed improvement ($\chi^2 = 2{\cdot}1$; $P > 0{\cdot}1$). The two patients in whom first rib excisions were performed following previous cervical rib excisions at other institutions had symptomatic improvement.

Table 3 lists the complications that occurred after surgery in eight patients (14 per cent). The numbness in the arm of two of the three affected patients resolved spontaneously. Reoperation was required for recurrence of symptoms in two patients who were initially thought to have been cured. The cause of symptoms was regrowth of a first rib in one patient; in the other, who had the Melkerson–Rosenthal syndrome, dense fibrous tissue was removed. Partial and total relief of symptoms occurred respectively. Two patients subsequently developed minor symptoms on the contralateral side but neither required surgical intervention.

Discussion

The resolution of symptoms of TOCS was first achieved surgically by excision of a cervical rib[1] and subsequently by excision of the first rib[2]. Controversy exists as to which technique is better at relieving symptoms in the presence of a cervical rib[3–5]. The incidence of cervical rib is 0·5–1 per cent[6] and cervical ribs are thought to cause symptoms in 2–35 per cent of affected individuals[7,8].

In contrast to other series[4,6,9], neurological symptoms were not the commonest presentation here. Patients with venous symptoms infrequently had a cervical rib[9]. Compared with other large series[10–12] fewer patients underwent rib excision for neurological symptoms. In these large series neurological symptoms were responsible for 95 per cent of cases, venous symptoms for 1–5 per cent and arterial symptoms for 0·5–2 per cent. Like the Southampton vascular surgical group[5] we had a preponderance of cases due to vessel compression, which may simply reflect the referral bias to a vascular unit.

All the patients have been followed up for a minimum of 2 years. This is especially relevant when looking at outcome, as it has been suggested that the mean time to recurrence of symptoms is 4 months, with 63 per cent of recurrences occurring within 6 months[13]. The effectiveness of treatment with improvement in over 90 per cent of patients is comparable with that of other series[4,5,7,10,14]. Both the Manchester[4] and Southampton[5] groups suggested that cervical rib excision alone is probably inadequate for the treatment of patients with vascular symptoms. All patients with vascular symptoms treated by first rib excision by the latter group had a degree of improvement[5]. Of the present patients with vascular involvement, all who had cervical rib excision showed improvement, whereas 90 per cent who had a first rib excision showed improvement. In such a small group the results cannot be shown statistically to be significantly different.

In the present series most early complications were secondary to opening the thoracic cavity; neurological complications occurred in three patients. These figures are comparable with those given in other major series[10–12]. The need for reoperation for symptoms in 3 per cent of patients compares well with quoted figures for reoperation of between 1 and 15 per cent[8,15,16].

The major problem in comparing series is that the results are described in terms of 'excellent', 'good' or 'partially relieved'[7]. This leads to the possibility of observer bias. Unfortunately, in view of the small numbers treated per annum even in large series, a prospective trial would be difficult.

In conclusion, as in the previous studies[4,5,7], it has been shown that surgery for TOCS is an effective method of relieving symptoms. The main difference in the present series is that patients with vascular symptoms associated with a cervical rib were adequately treated by cervical rib excision alone.

References

1. Coote H. Exostosis of the left transverse process of the seventh cervical vertebra surrounded by blood vessels and nerves: successful removal. *Lancet* 1861; **i**: 360.
2. Bramwell F. Lesion of the first dorsal nerve root. *Rev Neurol Psychiatry* 1903; **1**: 263.
3. Gilliat RW. Thoracic outlet compression syndrome. *Br Med J* 1976; **i**: 1274–5.
4. Brown SCW, Charlesworth D. Results of excision of a cervical rib in patients with the thoracic outlet syndrome. *Br J Surg* 1988; **75**: 431–3.
5. Thompson JF, Webster JHH. First rib resection for vascular complications of the thoracic outlet syndrome. *Br J Surg* 1990; **77**: 555–7.
6. Keen WW. The symptomatology, diagnosis and surgical treatment of cervical ribs. *Am J Med Sci* 1907; **133**: 173–9.
7. Halsted WS. An experimental study of circumscribed dilation of an artery immediately distal to a partially occluding band, and its bearing on the dilatation of the subclavian artery observed in certain cases of cervical rib. *J Exp Med* 1916; **24**: 271–7.
8. Adson AW, Coffey JR. Cervical rib. A method of anterior approach for relief of symptoms by division of the scalenus anticus. *Ann Surg* 1927; **85**: 839.
9. Porter JM, Taylor LM, Friedman EI. Cervical and first rib excisions. In: Greenhalgh RM, ed. *Indications for Vascular Surgery*. Philadelphia: Saunders, 1988: 101–16.
10. Roos DB. The place of scalenectomy and first-rib resection in thoracic outlet syndrome. *Surgery* 1982; **92**: 1077–83.
11. Stallworth JM, Quinn GJ, Aiken AF. Is rib resection necessary for relief of thoracic outlet syndrome? *Ann Surg* 1977; **185**: 581.

12. Dale WA, Lewis MR. Management of the thoracic outlet syndrome. *Ann Surg* 1975; **181**: 575–85.
13. Sessions RT. Reoperation for thoracic outlet syndrome. *J Cardiovasc Surg* 1989; **30**: 434–44.
14. Kelly TR. Thoracic outlet syndrome: current concepts of treatment. *Ann Surg* 1979; **190**: 657–62.
15. Sanders RJ, Monsour JW, Gerber WF, Adams WR, Thompson N. Scalenectomy *versus* first rib resection for treatment of thoracic outlet syndrome. *Surgery* 1979; **85**: 109–21.
16. Urschel HC, Razzuk MA, Albers JE *et al.* Reoperation for recurrent thoracic outlet syndrome. *Ann Thorac Surg* 1976; **21**: 19–28.

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Announcement

European Surgical Fellowships

Since 1990, the Council of *The British Journal of Surgery* has awarded European Fellowships, each holding a value of up to £3000. The first four successful applicants have now completed their Fellowships and Council has been pleased with the development of the scheme to date.

Mr R. Graeme Wilson used the opportunity to visit European centres developing laparoscopic techniques. Mr A. Ross Naylor used the opportunity to visit various vascular centres in Europe with particular reference to carotid artery surgery. Mr Ashley Dennison used the opportunity to visit a specialist hepatobiliary unit in Switzerland. Mr Colin D. Johnson took the opportunity to visit centres in Germany with a special interest in hepatobiliary and pancreatic surgery.

Three Fellowships have been awarded for 1991 to Mr B. J. Jenkins (London), Mr T. A. Lees (Newcastle-upon-Tyne) and Mr I. D. Anderson (Manchester).

Council are anxious to expand the scheme to allow surgeons working in other European countries to visit the UK. It is hoped that the candidates will use the Fellowships to visit surgical centres of their choice to extend their surgical experience. Fellowships will not be awarded solely for the purpose of attending courses or meetings.

It is Council's intention to offer European Fellowships once again in 1992. Applicants should submit details of their proposed itinerary and its anticipated costs, together with a curriculum vitae and two letters of support from senior colleagues. They should explain briefly how such a visit might broaden their experience and assist their career. Applications should be sent to the Company Secretary, Professor D. C. Carter, University Department of Surgery, Royal Infirmary, Edinburgh EH3 9YW by 31 January 1992.

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Current management of trauma to the pancreas

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This review examines pancreatic trauma and its management in the light of recent experience. The incidence, mechanism, classification, diagnosis, treatment and complications of pancreatic trauma are discussed. The difficulty in establishing the diagnosis is addressed and possible solutions are provided. The case for conservative surgery in the absence of pancreatic duct damage is outlined. The importance of draining all pancreatic injuries is emphasized.

Incidence and mechanism of injury

Injuries to the pancreas are uncommon. A recent study from Sweden[1] reported an incidence of only 0·4 per 100 000 population. Despite these figures, the serious nature of the injuries together with the relatively young age of most victims means that all surgeons should have at least a basic knowledge of the management of pancreatic trauma. There is a marked predominance of young men among those with pancreatic injury. A representative series of 93 patients with pancreaticoduodenal trauma revealed that 83 per cent of injuries involved men and that 78 per cent were in people less than 40 years old[2].

Damage to the pancreas is caused by either blunt or penetrating trauma. The blunt trauma mechanism of injury can be understood by considering the relationship of the pancreas to the vertebral column. Injury over the vertebral bodies tends to result in transection of the pancreas just to the left of the superior mesenteric vessels. Injuries to the right of the vertebrae may produce crushing of the pancreatic head and duodenum against the spine. Blunt injury to the left of the vertebrae may result in damage to the pancreatic tail and the spleen. In the UK, blunt trauma to the pancreas and duodenum is usually caused by road traffic accidents[3]. This region may be injured by direct contact with the steering wheel when the driver is unrestrained, or by incorrectly fitted lap components of seat belts. Handlebars may inflict similar injuries to motorcyclists and to children on bicycles. In view of the difficulties in clinical diagnosis, a high index of suspicion is necessary when a history of these forms of injury is obtained.

In North American cities, gunshot wounds and knife wounds are the two common causes of pancreatic trauma. In the UK, penetrating injuries are less common and pancreatic trauma usually arises after road traffic accidents. Because of this geographical variation in aetiology, there is also a wide variation in the incidence of pancreatic damage in abdominal trauma. This may range from under 1 per cent to 12 per cent.

Associated injuries

Isolated injuries to the pancreas are uncommon. There is a very high incidence of associated injuries, with figures of 50–98 per cent widely reported[4–15]. It is usual to find many organs injured in the same patient; the mean number[5,13] may range from 3·5 to 4·3. These associated injuries lead to most of the morbidity and mortality linked with pancreatic trauma. The liver, spleen, stomach, duodenum and colon are the organs most commonly injured[7]. Colonic injuries are more common after penetrating than after blunt trauma (27 *versus* 2 per cent), and are associated with a high incidence of postoperative sepsis. These penetrating injuries may also result in damage to retroperitoneal vessels in 50 per cent of cases[12].

Experimental pancreatic trauma

The literature on experimental pancreatic trauma is scanty. In 1943, Dragstedt showed that 80–90 per cent distal pancreatectomy in dogs resulted in neither endocrine nor exocrine insufficiency[16]. This correlates well with observations in humans after pancreatic resection. Most authors advise against reconstruction of transected pancreatic ducts. This is felt to be too difficult and time consuming to be of use in patients with severe associated injuries, and it has a high complication rate[17]. Lamesch and Dociu experimentally divided pancreatic ducts in dogs and then reconstructed them using microsurgical techniques[18]. There were no complications and all anastomoses remained patent. They attribute failure of conventional techniques of ductal reconstruction to failure to obtain a microscopically accurate anastomosis.

Classification of injuries

A number of classifications exist to describe pancreatic injuries. The system suggested by Lucas[19] is probably the most popular:

1. Simple superficial contusion with minimal parenchymal damage. Any portion of the pancreas can be affected but there is no damage to the pancreatic duct.
2. Deep lacerations, perforations or transection of the body or tail of the pancreas. The pancreatic duct may be damaged.
3. Severe crushing, perforation or transection of the head of the pancreas with or without ductal injury.
4. Combined pancreaticoduodenal injuries, subdivided into:
    - (a) those with mild pancreatic injury
    - (b) those with severe pancreatic injury and duct disruption.

A classification such as this is useful because surgical management varies with the type of injury.

Diagnosis

The diagnosis of pancreatic injury can be extremely difficult. Early diagnosis of blunt pancreatic injury is hampered by the retroperitoneal location of the organ. This diminishes the typical clinical features of peritonitis and thereby causes diagnostic delay. This in turn results in delay in laparotomy, which is the most important cause of increased morbidity and mortality rates. The minimal abdominal pain and tenderness presenting immediately after injury often decreases over the next 1–2 h only to worsen again within 6 h (Reference 19). This feature will result in a missed diagnosis unless a high index of suspicion is associated with recognition of the mechanism of injuries and repeated subsequent examination is carried out. In all gunshot wounds and some stab wounds to the abdomen a laparotomy is mandatory. Patients with abdominal stab wounds, without overt signs of visceral injury, undergo selective

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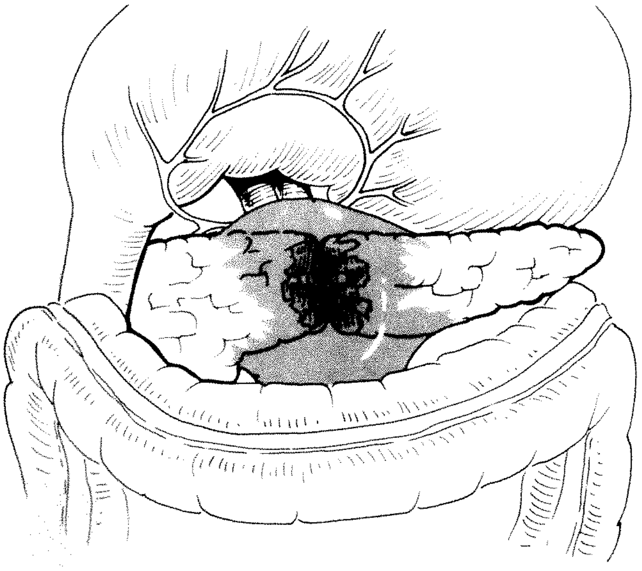

Figure 1 *Pancreatic haematoma with division of the main duct*

laparotomy based on local wound exploration and peritoneal lavage[20]. In these cases the diagnosis of pancreatic trauma should be made during operation. However, even at laparotomy, injuries to the pancreas may be missed, with potentially disastrous consequences. If pancreatic trauma is a possibility, there should be good visualization, mobilization and thorough examination of the gland and the adjacent duodenum.

If a haematoma around the pancreas is encountered it must be explored[4,21,22]. Failure to do so can result in missed injuries to the pancreatic duct[21] (*Figure 1*). The inexperienced surgeon should seek help before exploring such retroperitoneal haematomas as their release may result in uncontrollable haemorrhage.

Although contusions and lacerations to the pancreas are readily diagnosed, ductal damage can easily be missed even with thorough exploration. Because of this, some surgeons advocate intraoperative pancreatography to outline the main pancreatic duct[4,7]. Two methods exist for doing this. One is to amputate the tail of the pancreas and insert a cannula into the main duct. The more popular method is to cannulate the ampulla of Vater through a duodenotomy using a 5 Fr gauge paediatric feeding catheter. Sodium diatrizoate, 2–5 ml, is then injected to visualize the duct. No significant force should be used as this may produce postoperative pancreatitis. Advocates of this procedure claim a significant reduction in postoperative morbidity and mortality rates as duct injury will not be missed. In the series reported by Berni *et al.*[7], the rate of major complications dropped from 55 to 15 per cent and deaths from 11 to 0 per cent after the introduction of ductography.

Despite the obvious advantages of this technique, many are unhappy about performing a duodenotomy and risking potential fistulae. We believe that the theoretical risk of a duodenal fistula is outweighed by the real risk of late complications of missed ductal injuries. Although this remains controversial[11,12,23] we recommend the use of intraoperative pancreatography.

The diagnosis of pancreatic injury after blunt trauma can be particularly difficult. The presence of associated injuries may dictate management in the form of an exploratory laparotomy, when the procedures already outlined should be followed. It is when laparotomy is not necessarily required that the diagnosis of possible pancreatic injury becomes a problem.

Because of the retroperitoneal site of the pancreas, physical signs may be unhelpful. A plain abdominal radiograph should be taken to identify retroperitoneal air, which may be present in duodenal rupture. However, interpretation may be difficult and the yield of positive findings was only 18 per cent in a series of 152 cases[17]. Serum amylase measurement is generally unreliable as a diagnostic test; it may be more useful after operation as an indication of the development of complications[9]. In penetrating injuries, amylase levels may be elevated in only 8–23 per cent of cases[4,6,12]. Levels tend to be higher after blunt trauma, but the wide ranges reported (14–71 per cent) suggest that it is not a reliable indicator of trauma[4–6,12]. Even with complete pancreatic transection, amylase levels may be normal in 30–35 per cent of patients[4,12]. Hyperamylasaemia may also be caused by trauma to the head, face and chest, rupture of the stomach, duodenum or small bowel, acute alcohol intake, small bowel infarction, and hypotensive shock. The use of amylase isoenzymes has not resulted in an improvement in the diagnosis of pancreatic trauma[24].

Diagnostic peritoneal lavage, a useful tool in blunt abdominal trauma, is of little value in diagnosing pancreatic injury. False negative results are common, and so the investigation is limited to the detection of associated visceral injuries which frequently occur. However, a positive result from injury to another abdominal organ will allow identification of the pancreatic injury at subsequent laparotomy.

Computed tomography (CT) scanning is of more value in assessing the stable patient, but again its usefulness is limited. If the patient is scanned soon after injury, major trauma such as pancreatic fracture may not show up[25]. A CT scan may appear normal in 40 per cent of significant pancreatic injuries[26]. If scanning is performed, meticulous attention to detail is required to reduce false positive results. Unexplained thickening of the anterior renal fascia should alert the examiner to possible pancreatic trauma[25]. CT scanning in the acute stage may be more useful for diagnosing associated injuries[27].

Endoscopic retrograde cholangiopancreatography (ERCP), although advocated by some for stable patients[26,28,29], probably has no place in the acute situation because of its invasive nature[30]. ERCP and ultrasonographic scanning are of more value in the diagnosis of late problems arising from missed injuries[15,27].

Apart from intraoperative evaluation, most other means of detecting pancreatic trauma are unsatisfactory. A high index of suspicion is mandatory if pancreatic injury is not to be missed.

Operative management

The approach to patients with pancreatic trauma is similar to that used for any patient with serious abdominal injury. The history of injury and physical examination are exceedingly important and should proceed simultaneously with resuscitation. The ABC of primary survey must be performed: airway management, breathing, and circulatory evaluation. The upper airway must be cleared and protected, as must the cervical spine. If breathing is inadequate, the cause must be established while ventilation allowing adequate oxygenation is maintained. Venous access must be established and volume replacement carried out. Routine blood tests should include haemoglobin concentration, white cell count, packed cell volume, group and crossmatch, urea and electrolytes, and arterial blood gas estimation. A nasogastric tube will empty the stomach and prevent gastric dilatation. A urethral catheter is mandatory unless urethral injury is suspected, when the suprapubic route is used. The last two measures are essential before either peritoneal lavage or laparotomy is carried out.

A laparotomy through a long midline incision is needed. As with all trauma cases, the first priority is to arrest haemorrhage and then to limit any further gastrointestinal contamination, should any have occurred. When there are no other serious injuries, the pancreas is then examined.

The pancreas is best approached through the lesser sac via the gastrocolic omentum. The presence of retroperitoneal air, particularly around the head and duodenum, or free bile should be sought. Haematomas around the pancreas and duodenum should alert the operator to possible pancreaticoduodenal injury and these must be explored. The duodenum is fully

Kocherized, allowing examination of the pancreatic head and the retroperitoneal areas of the duodenum, where injuries can easily be overlooked. The whole of the pancreas must be fully visualized and thoroughly examined. Division of the gastrocolic omentum just outside the gastroepiploic arcade allows thorough inspection and palpation of the anterior surface and superior and inferior margins of the pancreas. Two approaches may be used to mobilize the tail of the pancreas. If the spleen is injured, the spleen and pancreas are mobilized medially by dividing the lienorenal ligament and areolar tissue along the superior and inferior margins of the pancreas. If the spleen is intact, the retroperitoneal tissue along the inferior margin of the pancreas is incised. The gland is then elevated, exposing its posterior surface.

Prophylactic antibiotics should be administered in cases of abdominal trauma[6,9,11,20,21,23]. In many American series these are given in the emergency room according to a management protocol. Although the choice of specific antibiotic differs, there is broad agreement on the indications. These include all patients with penetrating trauma (from either gunshot or stab wounds), and most authors include patients with blunt trauma who require laparotomy. Broad-spectrum antibiotics which will cover contamination from organisms present in the gut are used. One dose before operation should be followed by two doses thereafter unless there is colonic injury, in which case a therapeutic course for 5 days should be used[20]. If a splenectomy is performed with a distal pancreatectomy, prophylactic penicillin should be taken along with pneumococcal vaccine to reduce the risk of pneumococcal sepsis[31].

Management of the pancreatic wound depends on the type of injury.

Grade I and II injuries

Simple drainage alone is all that is necessary for grade I injuries. Sump drains are widely advocated as there is some evidence that these reduce postoperative complications[5]. They should be left in place for around 10 days[12]. In a series reported by Wynn *et al.*, 14 patients with grade I injuries were all treated by drainage[32]. There was no morbidity or mortality and the average hospital stay was 14 days. In another series of 23 patients, of whom 87 per cent were treated with drainage, there were four minor complications and no deaths[11]. Sorensen *et al.* reported 17 patients after penetrating trauma; there were seven complications in five patients and no deaths after drainage[33]. External drainage provides an excellent means of removal of pancreatic secretions. These contain activated proteolytic enzymes and may be destructive. Adequate drainage will diminish the formation of both fistulae and abscesses. Passive drains fail to prevent formation of pancreatic juice collections[5]. Straight suction drains become ineffective because of plugging by collapse of adjacent tissues. Sump drains provide almost complete evacuation of secretions and avoid local autodigestion. Several studies show marked falls in the complication rate on changing from routine use of passive drains to active sump drainage. Cogbill *et al.*[6] noted a fall from 64 per cent morbidity with passive drains to 36 per cent with sump drains. Stone *et al.*[5] demonstrated an even more marked fall in complication rate, from 39 to 2 per cent. Some combine the use of passive and active drainage and remove the sump drains at an earlier stage than the passive ones[9,11]. There are two main problems associated with the use of sump drains. First, they are rapidly colonized by hospital pathogens and may thus increase the rate of abscess formation. The use of a bacterial filter for the air going into the drain before it enters the body may decrease this risk[5]. Alternatively, a soft catheter may be placed down the formed tract of the sump drain after its removal at 10 days or later. This second tube is gradually withdrawn, allowing closure of the wound from below. Secondly, sump drains are rigid and may erode adjacent viscera or vessels. This risk may be diminished by the use of softer materials in drains or interposition of a leaf of omentum between the drain and surrounding tissues[20].

Drainage alone is adequate for grade II injuries if the main duct is intact. Suturing the parenchyma and capsule, although suggested by some surgeons[20,21], is unnecessary and may be dangerous. Capsular repair in the presence of a missed ductal injury may result in the development of a pseudocyst[19]. There is lower ultimate risk from the controlled fistula that would have been the outcome after drainage.

A variety of options exist to deal with pancreatic duct damage when it occurs in the body or tail, to the left of the mesenteric vessels. Repair of the duct should not be considered[17]. The best method for dealing with this problem is distal pancreatectomy and drainage[4–9,12,14,21,22,30,32] (*Figure 2*). Some suggest splenic preservation[34], but this involves a tedious dissection and added operation time, which could be considered inappropriate in an acute situation. There is also the possible late complication of splenic vein thrombosis.

Wynn *et al.* reported on 26 patients with grade II injuries[32]. Drainage was performed in 42 per cent, and 58 per cent underwent distal pancreatectomy. There were nine major complications in five patients and an 11 per cent mortality rate. The average hospital stay was 33 days. In 18 patients reported by Smego *et al.* there was one death; three fistulae and three intra-abdominal abscesses also occurred[11]. Their management was by drainage in 73 per cent and resection in 27 per cent. In contrast, Sorensen *et al.* used resection in 17 patients, 10 (59 per cent) of whom suffered a total of 24 complications. A solitary patient treated by drainage had no complications[33].

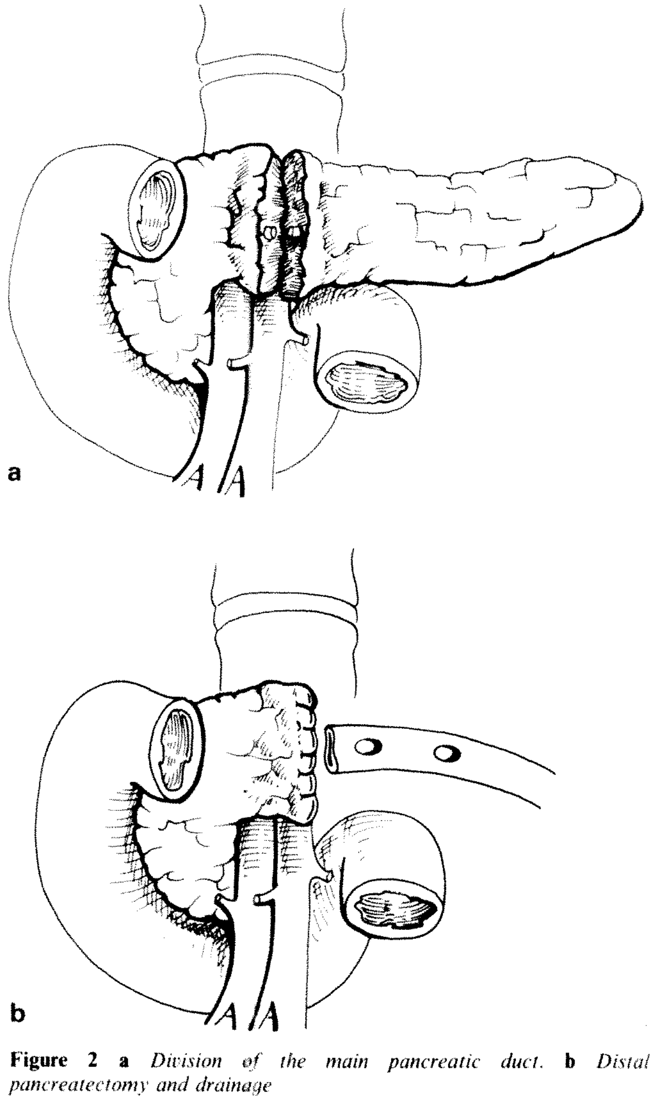

Figure 2 **a** *Division of the main pancreatic duct.* **b** *Distal pancreatectomy and drainage*

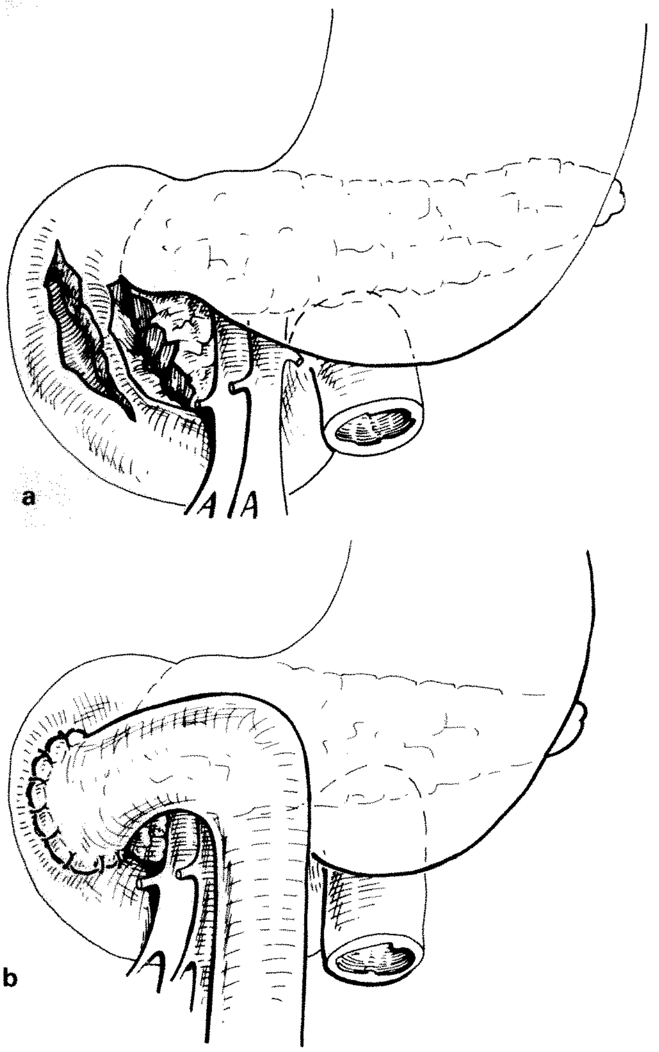

Figure 3 **a** *Combined pancreaticoduodenal injury.* **b** *Onlay Roux-en-Y loop to cover both injuries*

Grade III and IV injuries

Major injuries to the pancreatic head without ductal damage are best treated conservatively by sump drainage. If the duct is damaged, an onlay Roux-en-Y loop is probably the best procedure[21].

Smego *et al.* reported 14 patients with grade III injuries[11]. All had resections performed and there was one death; four fistulae and one intra-abdominal abscess also occurred. Wynn *et al.*[32] reported six patients of whom one died. One patient underwent a pancreaticoduodenectomy without complication, and the only patient treated by drainage developed a fistula. Three patients survived total or near-total pancreatectomy with duodenal diversion and had satisfactory long-term outcomes. The average hospital stay was 31 days. Sorensen *et al.* treated one patient with resection[33]. There were three major complications, but the patient survived. Their 6-year review contained 41 patients with penetrating abdominal trauma. Overall, 20 patients were treated with drainage, with an 11 per cent mortality rate and two pancreatic and six non-pancreatic complications. Twenty-one patients underwent resection, with a resultant 19 per cent mortality rate and 18 pancreatic and 16 non-pancreatic complications. The differences in morbidity and mortality rates could not be accounted for by the severity of the injury. They recommend drainage for the majority of penetrating pancreatic injuries and suggest that resection be reserved for injuries requiring debridement and for haemostasis.

Pancreaticoduodenectomy for grade IV injuries carries an unacceptably high mortality rate in the acute situation[32]. The reported overall mortality rate is 30–40 per cent. A Whipple's procedure should therefore be performed only in the most severe injuries where the missile has effectively performed the resection and the operation is essentially debridement of devitalized tissue. The incidence of such procedures is no more than 2 per cent[6]. Several less radical and more satisfactory options exist to deal with these sorts of injury:

1. Onlay Roux-en-Y loop to cover the damaged areas of adjacent pancreas and duodenum[21] (*Figure 3*).
2. Duodenal diversion. There are two ways of achieving this:
   (a) Pyloric exclusion[4,6,8,10,20,35]. After repair of the duodenotomy a 4 cm gastrotomy is made along the distal greater curve. Through this the pylorus is approached and a polyglactin (Vicryl®, Ethicon Ltd., Edinburgh, UK) purse-string suture is inserted to close the pylorus. A gastrojejunostomy is then constructed using the same gastrotomy (*Figure 4*). Vagotomy is not required because the pylorus should re-open and function normally after 3 weeks. It is the first 3 weeks after surgery that carry the high risk of fistulae[35].

   Vaughan *et al.* reported 75 patients undergoing pyloric exclusion for pancreaticoduodenal injury. The mortality rate was 19 per cent and there was a 12 per cent fistula rate. The complications attributable to the technique were two suture line bleeds and one case of gastric outlet obstruction[36]. There was free passage of contrast medium on 25 late follow-up radiological studies and 4 per cent had marginal ulcers. Cogbill *et al.* used the same technique but substituted polyglactin for chromic catgut sutures[6]. They reported one death among eight patients, two fistulae which closed spontaneously in 21 days, and no ulcers.

   (b) Duodenal diverticulization. This is a more extensive procedure requiring duodenal repair, vagotomy, antrectomy, gastrojejunostomy and tube duodenostomy (*Figure 5*). Although it has its supporters[4,8,22], it is a complex operation which may have no advantage over the simpler procedure of pyloric exclusion.

   Berne *et al.* described 50 trauma patients who underwent duodenal diverticulization[37]. They had a 16 per cent mortality rate, and all their fistulae at the site of the tube duodenostomy closed spontaneously.

   The results of duodenal diversion offer a significant improvement over primary repair and drainage. Fistula rates as low as 3 per cent have been reported using this

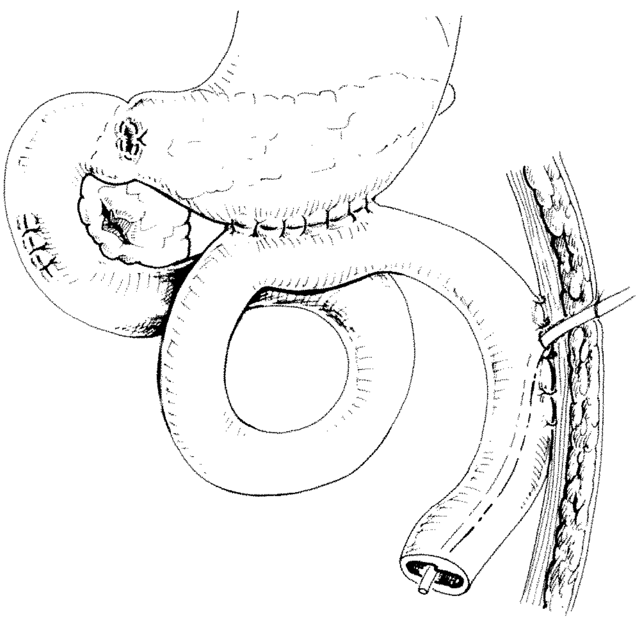

Figure 4 *Duodenal diversion with pyloric exclusion and feeding jejunostomy*

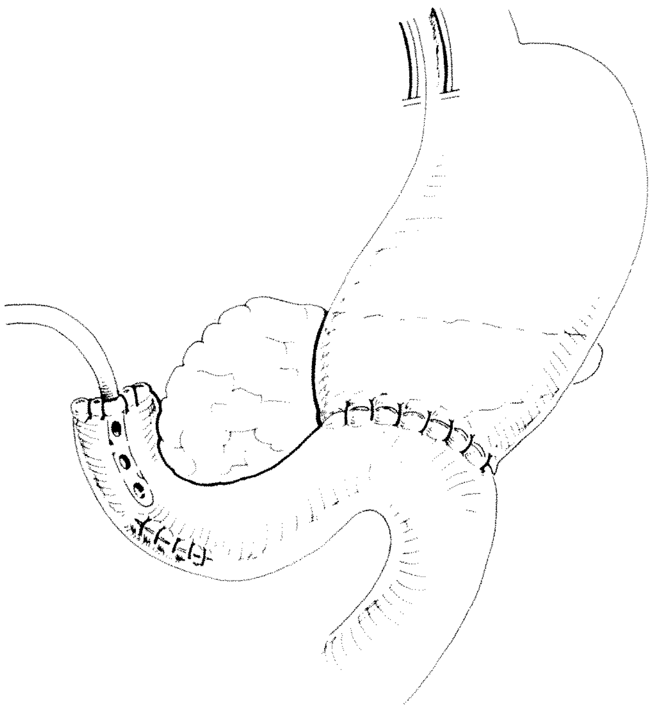

Figure 5 *Duodenal diverticulization*

technique[20]. Both pyloric exclusion and duodenal diverticulization are designed to divert the stream of gastric contents away from the duodenum. This should allow healing and decrease pancreatic and biliary secretions. They offer the advantage of a quicker and technically easier operation, lower mortality rate and no loss of pancreatic tissue in comparison with pancreaticoduodenectomy. Duodenal diversion should be used unless the pancreas and duodenum are devitalized.

Sorensen *et al.* described five patients with grade IV injuries[33]. Two underwent drainage with only one complication; a patient treated by simple drainage needed re-exploration for bleeding, and a patient treated by duodenal diversion had no complications. Three patients with resections had seven major complications. One of the two who had a total pancreatectomy died at operation, but the other, and a patient who had a pancreaticoduodenectomy, survived. There was a 100 per cent mortality rate in six patients reported by Wynn *et al.*[32]. Three patients exsanguinated in theatre, and the other three survived an average of 45 days. One patient with duodenal diverticulization died from a pulmonary embolus after suffering a duodenal fistula. Both patients who had a pancreaticoduodenectomy died, one from sepsis and bleeding and the other after an anastomotic breakdown. Drainage of pancreatic injuries is particularly important. Whatever the type of injury, a sump drain should always be used[5,6,11,20,32,35,38].

Nutritional support

Nutrition after surgery is important in the management of pancreatic injuries, particularly combined pancreaticoduodenal ones. It may be some considerable time before normal oral feeding can be reintroduced. The average time that nutritional support was required in the series reported by Wynn *et al.* was 14 days (range 2–43 days). Some use total parenteral nutrition (TPN), with its combined effect of providing nutrition and reducing pancreatic secretion[38]. Most, however, advocate feeding jejunostomies in the postoperative period[6,20,35] (*Figure 4*). Enteral nutrition is safer[39], cheaper[40], more physiological[41], and associated with less stress ulceration and fewer other complications than TPN[42]. Enteral provision of an elemental diet distal to the pylorus has the same suppressant effect on pancreatic secretions as intestinal rest and TPN[43]. A comparison between enteral and parenteral hyperalimentation using the same solution has been reported in 24 patients[44]. This showed that enteral feeding requires less insulin than TPN to maintain normoglycaemia and that it is more efficient for nitrogen utilization, both advantageous features for those with pancreatic trauma. The enteral route may also be more effective in restoring immune competence. Kudsk *et al.* reported that enteral feeding was more effective than parenteral feeding in preventing septic complications in protein-depleted rats[45]. Mansour *et al.* suggest that a feeding jejunostomy may be used for feeding in outpatient management of a persistent pancreatic fistula[35].

Complications

Morbidity rates are high and vary according to the nature of associated injuries. Complication rates range from 30 to 64 per cent[6,7,9,11–15,20,32]. Spay has described the long-term surveillance of 23 patients after isolated pancreatic injury[46]. There were five cases of diabetes, two of exocrine insufficiency and two of combined endoexocrine insufficiency.

Fistula

This is the commonest complication arising from pancreatic trauma. The incidence may be from 7 to 20 per cent[5,20,47], rising to 26 per cent after combined pancreaticoduodenal injury[12]. Most develop within the first 3 weeks and can be anticipated if a major duct injury is not properly dealt with. Generally, fistulae are more common after injuries to the pancreatic head. Stone *et al.* noted that, of their 19 fistulae in 275 patients, 58 per cent were in the head, 26 per cent in the body and 16 per cent in the tail[5]. Smego *et al.* demonstrated that the frequency of pancreas-related complications increased with the grade of injury[11]. Abscess or fistula was seen in 9 per cent of grade I injuries, 17 per cent of grade II injuries, 36 per cent of grade III injuries and 50 per cent of grade IV injuries. The rate of fistula formation also varies with the method of management. In a series of 450 patients reported by Jones, fistulae were seen in 3 per cent of those treated by drainage, 4 per cent of those treated by distal pancreatectomy and 20 per cent of those treated by duodenal diverticulization[12].

Fistulae may drain up to 1000 ml/day depending on size. If the diagnosis is in doubt, the amylase content of the fluid should be measured. Most fistulae can be managed conservatively. This involves good drainage, protection of the skin, and nutritional support. There must be careful attention to fluid and electrolyte balance. A biochemical assay of the electrolytes in fistulous losses is useful. Each litre of fluid lost must be replaced with a litre of normal saline. Supplemental replacement of potassium, bicarbonate and (in prolonged cases) zinc and magnesium may be necessary. Of the 28 fistulae reported by Feliciano *et al.*[23], 70 per cent closed in 2 weeks, and the slowest in 12 weeks. Recently, a somatostatin analogue has been used to hasten the closure of external pancreatic fistulae. This may be administered either as an intravenous infusion with TPN[48], or as a twice-daily subcutaneous injection[49]. The patients involved all had fistulae resulting from pancreatic surgery. We recommend a trial of somatostatin use in fistulae of traumatic origin. Surgery is rarely necessary to deal with this problem. In many series all fistulae closed spontaneously, and the maximum rate of reoperation was 7 per cent[5,6,11,12,20–23,35]. If operation is necessary, a Roux-en-Y loop to the offending area of the pancreas is the best treatment.

Abscess

The incidence of abscess formation after pancreatic trauma ranges from 10 to 25 per cent[5,6,11,12,20,22,23,32,35]. Abscesses usually develop as a result of associated injuries to adjacent viscera, and their frequency is dependent on which other organs are damaged[6,12,23]. This complication carries a high risk of death unless it is diagnosed and drained early[6]. In a series of 84 patients with pancreatic trauma, Wynn *et al.* reported postoperative abscesses in 19 patients, of whom 11 required exploration and drainage[32]. Ultrasonography and CT scanning were very useful in the early detection and localization of these abscesses. The mortality rate in this group was 20 per cent and the average hospital stay was 42 days. Feliciano *et al.* described 108 patients, of whom 18 (17 per cent) developed intra-abdominal abscesses. They all required percutaneous drainage or reoperation. Five patients subsequently died from multiple organ failure. There was a mean of 5·2 intra-abdominal visceral or vascular injuries in this group.

Pancreatitis

The development of pancreatitis after pancreatic trauma is a common and serious complication and may carry a high risk of death[5,6,11,20]. Stone *et al.* reported a series of 283 patients in which pancreatitis resulted in eight of 39 deaths and 11 of 54 local complications[5]. The mortality rate varies depending on the severity of the pancreatitis. One series reported six cases of pancreatitis in 32 patients, all of which resolved[20], whereas five of six patients with haemorrhagic pancreatitis died in a series reported by Jones[12]. The treatment is the same as for any patient with pancreatitis, consisting of nasogastric suction, bowel rest and nutritional support.

Pseudocyst

With early diagnosis and treatment of pancreatic trauma, the incidence of pseudocyst should be only 2 per cent[5,6,12,20,35,47]. The rate depends on the adequacy of control of pancreatic secretions achieved by internal or external drainage or resection. In the series reported by Stone *et al.*, the incidence of pseudocyst varied from 7 per cent in patients treated with passive drainage, through 3 per cent in patients treated with distal resection, to 1 per cent in those treated with sump drainage[5].

Postoperative haemorrhage

This occurs in 5–10 per cent of cases[6,20,35]. Injuries to the pancreas alone do not generally result in major haemorrhage. After trauma, leakage of pancreatic juice or abscess development may result in erosion of an adjacent vessel, resulting in major haemorrhage. Emergency operative intervention was required in 75–100 per cent of cases of bleeding reported in two series[6,20].

Wound sepsis

The incidence of this is between 10 and 39 per cent. The rate varies according to the nature of any associated injuries and is particularly common with colonic involvement[6,12].

Exocrine and endocrine insufficiency

Either problem is unusual after pancreatic trauma. The amount of residual pancreatic tissue required to maintain exocrine and endocrine function is around 10–20 per cent in humans and in animal models[7,16]. In a series of 30 patients reported by Balasegaram, no pancreatic insufficiency occurred after up to 90 per cent resection[17].

Death

Isolated pancreatic injuries are uncommon and carry mortality rates of between 3 and 10 per cent[5,12]. Mortality rates are generally higher when associated injuries are present. The magnitude varies considerably in the literature. Some report rates as high as 22 per cent with penetrating injuries, compared with 19 per cent for blunt injuries[12]. The type of injury to the pancreas, presence and type of associated injuries, and the cause of injury (e.g. high-velocity gunshot wound compared with stab wound) are important variables to consider when making any literature comparison. In a 30-year review of 283 patients reported by Stone *et al.*, the overall mortality rate was 14 per cent[5]. Shotgun wounds carried a 67 per cent mortality rate, blunt injuries 17 per cent, other gunshot wounds 11 per cent and stab wounds 6 per cent. Trauma to the pancreatic head had a mortality rate of 20 per cent, compared with 12 per cent for the body and 10 per cent for the tail. This is probably because of the higher incidence of trauma to the duodenum and major vascular structures associated with wounds adjacent to the pancreatic head. The number of associated injuries also affects the mortality rate. Balasegaram reported a 2·5 per cent mortality rate with no or one associated injury, 13·6 per cent with two or three, and 29·6 per cent with four or more[17]. The mean mortality rate from reports over the last 10 years is 19 per cent with a range of 9–34 per cent[4,6–9,12–15,20,22,35,47]. Most deaths are due to haemorrhage and shock and occur within the first 24–48 h. In the series reported by Jones[12], 68 of 104 deaths (65 per cent) from pancreatic trauma occurred within 48 h. Later deaths are usually caused by sepsis or pulmonary complications.

Diagnosis and management of late presentations of pancreatic injury

Late complications of undetected trauma may present months to years after injury and can be difficult to manage[15,28,46].

Chronic pancreatitis usually arises because of either overlooked pancreatic trauma or missed ductal injury even when trauma was recognized. A careful history is needed to identify trauma as the aetiological factor, as presentation up to 21 years after injury has been reported[15]. Diagnosis of the extent of the pancreatitis and the integrity of the duct is best made by a combination of ultrasonography, CT scanning and ERCP[15,28]. A definitive operation to avoid further complications may then be planned. Satisfactory results were obtained by distal pancreatectomy in four such patients reported by Leppaniemi *et al.*[15] and four reported by Carr *et al.*[28].

Pancreatic fistulae, abscesses and pseudocysts are well documented complications of blunt and penetrating trauma. The failure of a disrupted ductal system to heal will result in ongoing leakage of activated proteolytic enzymes and tissue damage.

Incomplete duct transection may also result in a stricture after fibrous healing. Carr *et al.* reported a series of 11 patients with late complications[28]. These included five pseudocysts, one fistula, one abscess and four cases of recurrent pancreatitis. Ten of these patients had either strictures or disruptions of the main duct demonstrated on ERCP, ultrasonographic scanning or exploration. Pseudocyst accounted for 45 per cent of the late complications referred to this specialist unit, all of which required distal pancreatectomy after investigation revealed a disrupted ductal system[28].

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References

1. Nilsson E, Norrby S, Skullman S, Sjodahl R. Pancreatic trauma in a defined population. *Acta Chir Scand* 1986; **152**: 647–51.
2. Levison MA, Petersen SR, Sheldon GF *et al.* Duodenal trauma: experiences of a trauma center. *J Trauma* 1984; **24**: 475–80.
3. Flint LM, McCoy M, Richardson JD *et al.* Duodenal injury: analysis of common misconceptions in diagnosis and treatment. *Ann Surg* 1980; **191**: 697–702.
4. Dickerman RM, Dunn EL. Splenic, pancreatic and hepatic injuries. *Surg Clin North Am* 1981; **61**: 3–16.
5. Stone HH, Fabian TC, Satiani B, Turkleson ML. Experiences in the management of pancreatic trauma. *J Trauma* 1981; **21**: 257–62.
6. Cogbill TH, Moore EE, Kashuk JL. Changing trends in the management of pancreatic trauma. *Arch Surg* 1982; **117**: 722–8.

7. Berni GA, Bandyk DF, Oreskovich MR, Carrico CJ. Role of intraoperative pancreatography in patients with injury to the pancreas. *Am J Surg* 1982; **143**: 602–5.
8. Henarejos A, Cohen DM, Moossa AR. Management of pancreatic trauma. *Ann R Coll Surg Engl* 1983; **65**: 297–300.
9. Sims EH, Mandal AK, Schlater T, Fleming AW, Lou MA. Factors affecting outcome in pancreatic trauma. *J Trauma* 1984; **24**: 125–8.
10. Hendel R, Rusnak CH. Management of pancreatic trauma. *Can J Surg* 1985; **28**: 359–61.
11. Smego DR, Richardson JD, Flint LM. Determinants of outcome in pancreatic trauma. *J Trauma* 1985; **25**: 771–6.
12. Jones RC. Management of pancreatic trauma. *Am J Surg* 1985; **150**: 698–704.
13. Nowak MM, Baringer DC, Ponsky JL. Pancreatic injuries: effectiveness of debridement and drainage for nontransecting injuries. *Am Surg* 1986; **52**: 599–602.
14. Keeling P, Calthorpe D, Lane B, Collins PG. Blunt trauma to the pancreas: a report of 10 cases. *Ir J Med Sci* 1986; **155**: 431–5.
15. Leppaniemi A, Haapiainen R, Kiviluoto T *et al.* Pancreatic trauma: acute and late manifestations. *Br J Surg* 1988; **75**: 165–7.
16. Dragstedt LR. Some physiologic problems in surgery of the pancreas. *Ann Surg* 1943; **118**: 576–93.
17. Balasegaram M. Surgical management of pancreatic trauma. *Curr Probl Surg* 1979; **16**: 1–59.
18. Lamesch AJ, Dociu N. Microsurgical reconstruction of pancreatic ducts in dogs. *Surgery* 1986; **100**: 121–5.
19. Lucas CE. Diagnosis and treatment of pancreatic and duodenal injury. *Surg Clin North Am* 1977; **57**: 49–65.
20. Moore JB, Moore EE. Changing trends in the management of combined pancreatoduodenal injuries. *World J Surg* 1984; **8**: 791–7.
21. Campbell R, Kennedy T. The management of pancreatic and pancreaticoduodenal injuries. *Br J Surg* 1980; **67**: 845–50.
22. Fitzgibbons TJ, Yellin AE, Maruyama MM, Donovan AJ. Management of the transected pancreas following distal pancreatectomy. *Surg Gynecol Obstet* 1982; **154**: 225–31.
23. Feliciano DV, Martin TD, Cruse PA *et al.* Management of combined pancreatoduodenal injuries. *Ann Surg* 1987; **205**: 673–80.
24. Bouwman DL, Weaver DW, Watt AJ. Serum amylase and its isoenzymes: a clarification of their implications in trauma. *J Trauma* 1984; **24**: 573–8.
25. Jeffrey RB Jr, Federle MP, Crass RA. Computed tomography of pancreatic trauma. *Radiology* 1983; **147**: 491–4.
26. Barkin JS, Ferstenberg RM, Panullo W *et al.* Endoscopic retrograde cholangiopancreatography in pancreatic trauma. *Gastrointest Endosc* 1988; **34**: 102–5.
27. Kaude JV, McInnis AN. Pancreatic ultrasound following blunt abdominal trauma. *Gastrointest Radiol* 1982; **7**: 53–6.
28. Carr ND, Cairns SJ, Lees WR, Russell RC. Late complications of pancreatic trauma. *Br J Surg* 1989; **76**: 1244–6.
29. Whittwell AE, Gomez GA, Byers P *et al.* Blunt pancreatic trauma: prospective evaluation of early endoscopic retrograde pancreatography. *South Med J* 1989; **82**: 586–91.
30. Keeling P, Calthorpe D, Lane B, Collins PG. Blunt injury of the neck of the pancreas: a report of nine patients. *Injury* 1987; **18**: 93–5.
31. Pickhardt B, Moore EE, Moore FA *et al.* Operative splenic salvage in adults: a decade perspective. *J Trauma* 1989; **29**: 1386–91.
32. Wynn M, Hill DM, Miller DR *et al.* Management of pancreatic and duodenal trauma. *Am J Surg* 1985; **150**: 327–32.
33. Sorensen VJ, Obeid FN, Horst HM *et al.* Penetrating pancreatic injuries 1978–1983. *Am Surg* 1986; **52**: 354–8.
34. Pachter HL, Hofstetter SR, Liang HG *et al.* Traumatic injuries to the pancreas: the role of distal pancreatectomy with splenic preservation. *J Trauma* 1989; **29**: 1352–5.
35. Mansour MA, Moore JB, Moore EE, Moore FA. Conservative management of combined pancreatoduodenal injuries. *Am J Surg* 1989; **158**: 531–5.
36. Vaughan CD, Frazier OH, Graham DY *et al.* The use of pyloric exclusion in the management of severe duodenal injuries. *Am J Surg* 1977; **134**: 785–90.
37. Berne CJ, Donovan AJ, White EJ *et al.* Duodenal 'diverticulization' for duodenal and pancreatic injury. *Am J Surg* 1974; **127**: 503–7.
38. Robey E, Mullen JT, Schwab CW. Blunt transection of the pancreas treated by distal pancreatectomy, splenic salvage and hyperalimentation: four cases and review of the literature. *Ann Surg* 1982; **196**: 695–9.
39. Padberg FT, Rugerrio J, Blackburn GL *et al.* Central venous catheterization for parenteral nutrition. *Ann Surg* 1981; **193**: 264–70.
40. Page CP, Carlton PK, Andrassy RJ *et al.* Safe, cost-effective postoperative nutrition. *Am J Surg* 1979; **138**: 940–5.
41. Lickley HLA, Track NS, Vranic M *et al.* Metabolic responses to enteral and parenteral nutrition. *Am J Surg* 1978; **135**: 172–6.
42. Pingleton SK, Hadzima SK. Enteral alimentation and gastrointestinal bleeding in mechanically ventilated patients. *Crit Care Med* 1983; **11**: 13–16.
43. Ragins HM, Levenson SM, Signer R *et al.* Intrajejunal administration of an elemental diet at neutral pH avoids pancreatic stimulation. *Am J Surg* 1973; **126**: 606–14.
44. McArdle AH, Palmason C, Morency I *et al.* A rationale for enteral feeding as the preferable route for hyperalimentation. *Surgery* 1981; **90**: 616–21.
45. Kudsk KA, Carpenter G, Petersen S *et al.* Effect of enteral and parenteral feeding in malnourished rats with *E. coli*–haemoglobin adjuvant peritonitis. *J Surg Res* 1981; **31**: 105–10.
46. Spay G. Consequences lointaines des traumatismes du pancreas: vingt-trois observations. *Presse Med* 1986; **29**: 1374–5.
47. Whalen GF, Robbs JV, Baker LW. Injuries of the pancreas and duodenum: results of a conservative approach. *S Afr J Surg* 1987; **25**: 15–18.
48. Pederzoli P, Bassi C, Falconi M *et al.* Conservative treatment of pancreatic fistulas with parenteral nutrition alone or in combination with continuous intravenous infusion of somatostatin, glucagon or calcitonin. *Surg Gynecol Obstet* 1986; **163**: 428–32.
49. Prinz RA, Pickleman J, Hoffman JP. Treatment of pancreatic cutaneous fistulas with a somatostatin analog. *Am J Surg* 1988; **155**: 36–42.

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Review

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Impact of duplex scanning on vascular surgical practice

This review outlines the development of duplex scanning over the past 15 years and its value not only in vascular medicine and surgery but also in the field of transplantation and obstetrics. It is now the first line of investigation of patients with symptomatic carotid bifurcation disease and those with clinically suspected acute deep venous thrombosis. It is also an established method of femoropopliteal and femorodistal arterial graft surveillance, determination of the extent and cause of chronic venous insufficiency, detection of placental insufficiency and porta-systemic shunt patency, early transplant monitoring, as well as of detecting an arterial stenosis suitable for angioplasty. In addition, it is developing into the method of choice for the initial investigation of patients with suspected mesenteric or renal artery stenosis. The accuracy of duplex scanning, avoiding further unnecessary invasive and expensive diagnostic procedures, makes it one of the most cost-effective investigations ever introduced into clinical practice. Also, when used as a screening technique in arterial and venous disease, it selects those patients who need more invasive procedures such as angiography. This helps to reduce waiting lists of patients requiring investigation, and better directs limited resources to treatment rather than investigation.

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Arterial and venous surgery owe a great deal to technological developments over the past 40 years. Before the development of angiography and venography, the vascular surgeon was as 'blind as a mole' (from a speech read before Edwin J. Wylie at a dinner given in his honour in Boston, June 1975: 'Angiograms are the eyes of a vascular surgeon; without them, he becomes a mole'), relying on his fingers to guide him. Venography and arteriography, developed in the 1940s and 1950s, enabled him to see for the first time the outline of the vessel lumen. However, it soon became clear that anatomical information alone was not enough, and objective functional information was needed to complete the picture. Thus, in an attempt to make up for the shortcomings of angiography, a number of isotope clearance and plethysmographic techniques were developed. These have now been largely superseded by the development of duplex scanning. The purpose of this review is to examine the development of duplex scanning and its role in modern practice.

Development of duplex scanning

The 1970s saw the development of a major new technology, namely ultrasonography, and soon two important ultrasonic techniques were added to the diagnostic armoury of the vascular surgeon: B-mode imaging and Doppler ultrasonography.

All currently used ultrasonic techniques are variations of echo-ranging devices. A pulse is generated and travels through a medium until it strikes a barrier (interface). At that point a portion of the pulse is reflected back and the time elapsed from emission to reception is used to calculate the distance from the barrier to the sound source. In B-mode ultrasonography, each reflection is represented on the screen as a dot, the brightness of which depends on the amplitude of the returning echo. The picture is built up from the multiple reflections. In real-time ultrasonography, retrieved ultrasonic information is updated at a rate that is rapid enough to allow visualization of physiological motion within the field of view (over 15 frames per second is perceived as continuous by the eye)[1]. B-mode imaging was initially developed as an imaging procedure for obstetrics but soon became the method of choice for assessing the size and enlargement of the abdominal aorta in aneurysmal disease[2]. Subsequent improvement in resolution and the provision of real-time imaging have widened its application. Despite this, B-mode imaging suffers the same constraints as angiography; it is able to supply only anatomical information.

Doppler ultrasonography uses the Doppler effect; this is the phenomenon by which the frequency of a wave received after reflection by a moving target is shifted from that of the source. The classic example of this is the change in pitch of a train's whistle as it passes a stationary listener. By detecting velocity in distal arteries, continuous wave Doppler ultrasonography allows the measurement of ankle artery pressures, the recording of blood velocity wave forms, and the detection of venous reflux, but it has two major drawbacks. First, it insonates all tissues and provides simultaneous superimposed signals from all vessels in its path. Second, the angle between probe and vessel cannot easily be determined, thus preventing the conversion of Doppler shift signals into units of absolute velocity. A plethora of indices relating to continuous wave Doppler ultrasonography have been developed (pressure index, pulsatility index, Pourcelot index, Laplace transform function, resistance index), whose purpose has been to provide objective, non-invasive functional information. In 1974, the duplex scanner was created by the combination of real-time ultrasonic imaging and gated Doppler ultrasonography[3]. By altering (i.e. gating) the interval between an emitted burst of ultrasound and the time of listening for the reflected echoes, ultrasonic sampling of the Doppler effect could be accomplished at different depths and positions within tissues, determined by the gating selected by the operator. A further advantage of the duplex scanner was that by imaging the tissues it permitted the measurement of the angle of insonation in relation to the axis of the vessel, allowing calculation of absolute velocity, generally expressed in cm/s.

The first generation of duplex scanners was developed in the 1970s to detect and grade carotid bifurcation disease[4]. By the early 1980s, a second generation of duplex scanners had been developed which had a superior image quality. Also, the

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size of the Doppler sample could be varied so that insonation across the whole lumen of the vessel became possible (wide gate) with automatic calculation of the angle of insonation, mean Doppler shift and automatic expression of the result in cm/s (Reference 5). In addition, low frequency probes (2·5–3 MHz) enabled the study of the abdominal vasculature. This second generation of instruments was more versatile and the operator was not limited to insonating a vessel to a standard angle, usually 60°. This period saw the application of duplex scanning to many vessels throughout the body.

Colour flow imaging

One of the advantages of duplex scanning over simple ultrasonic imaging is its ability to detect fresh thrombus and plaque with the same echogenicity as blood. These may be detected by recording the haemodynamic disturbance produced by such a thrombus or wall irregularity. In the carotid arteries this is relatively quick and easy. However, in long vessels the detection of a high velocity jet indicating a stenosis requires sampling at regular intervals along the vessel lumen, a process that is tedious and time-consuming. This problem has been overcome by the third generation of instruments which provide real-time colour flow imaging superimposed on real-time grey scale imaging. The use of phased array transducers and microchip technology provides a means of testing every pixel on the screen for Doppler shift. Any movement may be depicted as colour, in general red for flow in one direction and blue for the reverse, and the higher the frequency of the Doppler shift, the whiter the colour depicted. Absence of colour indicates absence of flow. The colour flow map is superimposed on the real-time grey scale image such that an artery may appear as a pulsating red lumen, a thrombus or atherosclerotic plaque as a black area protruding into the lumen, and a tight stenosis as a white jet[5]. With colour flow imaging, rapid visual localization of the problem area allows the sample volume to be quickly positioned at the point of maximum disturbance so that velocity and diameter may be measured (and flow calculated automatically). As yet, the reproducibility and clinical usefulness of such flow measurements have not been fully evaluated.

A duplex scanner with colour flow imaging facility, although approximately twice as expensive as conventional black and white scanners, is three to four times quicker to use. Because more patients can be studied per session, the instrument is more cost-effective. Colour flow imaging allows follow-up studies to be performed safely and quickly at regular intervals, holding the promise of a future better understanding of the pathophysiological changes in arterial disease.

Duplex scanning for cerebrovascular disease

At present, duplex scanning is the method of choice for screening for suspected extracranial cerebrovascular disease[6,7]. It has replaced most of the indirect tests such as bruit analysis, oculoplethysmography and periorbital Doppler ultrasonography velocity studies, because duplex scanning allows both functional and anatomical information to be achieved in a single study. In addition to the detection and grading of stenoses, the high resolution imaging achieved with modern day linear transducers allows plaques to be characterized and intraplaque haemorrhage to be detected[8,9]. Duplex scanning has provided information on the natural history of patients with asymptomatic carotid disease and has allowed the identification of a high-risk group. As a result, it is now known that stenosis of <80 per cent carries a 1–3 per cent risk of producing a stroke, whereas stenosis of >80 per cent carries a stroke risk of 4–12 per cent per annum[10–13]. The risk is greater still if, in the presence of a stenosis of >80 per cent as detected by the peak systolic flow, the end-diastolic flow in the stenosis causes a Doppler shift of >200 cm/s (Reference 14). Such a high diastolic velocity indicates the presence of a high pressure gradient as a result of poor collateral circulation.

Duplex scanning may also be used to examine the subclavian, the innominate and the origin of the vertebral artery[15] during their course through the supraclavicular fossa. In this region, a stenosis of >50 per cent can be identified with a sensitivity of 88 per cent and a specificity of 98 per cent[16]. Colour flow facilitates the identification of the vertebral arteries at their origin and enables them to be followed along their course between the transverse processes to the base of the skull. With colour flow imaging, the diagnosis of subclavian steal is made easier as retrograde flow in the vertebral artery appears blue, i.e. the opposite to the carotid which is red; also, when the peripheral resistance of the arm is reduced by releasing a clenched fist, the steal is increased causing the frequency of the Doppler shift to increase. One of the drawbacks in the examination of the subclavian, innominate and vertebral arteries is that only certain portions of vessels may be visualized through the supraclavicular fossa.

Duplex scanning of the aorta and its branches

At present, with the exception of the ascending aorta, the supradiaphragmatic aorta is relatively inaccessible to duplex scanning. Below the diaphragm, the aorta is easily accessible to ultrasonography and, in the past 15 years, this method of examination has become common practice in the monitoring of aneurysmal dilatation[2]. Duplex scanning has recently been applied to this area. The aorta has a characteristic Doppler spectral pattern with a clear window in systole, indicating flow at a single velocity across the entire vessel. Pathological widening or narrowing of the aorta induces changes in the spectrum and aneurysmal dilatation results in flow separation and turbulence. This is seen particularly well with colour flow imaging. Also, the ability to show the extent of flow makes this a suitable method with which to demonstrate the true lumen of a dissecting aneurysm or to map thrombus that may not be apparent on a B-mode image.

Duplex scanning of the peripheral vascular tree

Until recently, arteriography was considered the gold standard in the assessment of the anatomy of the peripheral vascular system, complemented by a variety of non-invasive tests to assess the haemodynamics. Following improvement in the resolution of the B-mode image, duplex scanning is being used increasingly in the assessment of peripheral vascular disease. Duplex scanning has been shown to differentiate between haemodynamically significant and insignificant lesions in the aortoiliac and femoropopliteal arteries reliably, and has the potential to replace angiography. In a study comparing duplex scanning with intra-arterial digital subtraction angiography, Legemate and his colleagues have shown that a stenosis of >50 per cent in diameter could be detected with a sensitivity of 92 per cent and a specificity of 98 per cent for the aortoiliac segment, and 88 per cent and 98 per cent respectively for the femoropopliteal segment[17]. Duplex scanning of the peripheral vasculature is slow and time-consuming. The examination is much faster with the colour flow duplex. Colour flow imaging can accurately identify the presence and extent of occlusions in 94 per cent of cases when compared with angiographic and operative findings. In the diagnosis of stenosis of >50 per cent, a specificity of 87 per cent (compared with the 99 per cent for arteriography) has been obtained. This means that a decision to refer a patient for angioplasty may be made without an angiogram[18]. Duplex scanning may also be used before operation to assess the adequacy of the long saphenous vein for use as a bypass graft with an accuracy of 90 per cent[19].

Intraoperative scanning

A duplex scanner, because of its relative mobility, lends itself to use in the operating theatre. Intraoperative duplex scanning is now replacing intraoperative angiography after carotid endarterectomy[20,21], infrainguinal bypass grafting and mesenteric or renal reconstructive procedures. Wall defects that warrant immediate surgical correction have been demonstrated in 5 per cent of internal carotid arteries following endarterectomy and 7 per cent of renal and visceral reconstructions. Retained valves and anastomotic defects occur in 5 per cent of *in situ* saphenous vein bypass grafts, and prompt action as a result of intraoperative diagnosis can reduce the incidence of early graft failure. Using colour flow imaging, a carotid endarterectomy site can be scanned in 5 min and an *in situ* saphenous vein arterial bypass in 10 min. This technique is not only safer than angiography but also quicker, and can be repeated as necessary.

Postoperative surveillance

Stenotic narrowing develops in 25 per cent of infrainguinal vein grafts; unchecked, this may lead to premature graft occlusion. The postoperative monitoring of infrainguinal grafts allows early detection of stenosis and therefore the possibility of early intervention with a likely improvement in graft patency rates; whereas graft failure might result in amputation, a stenosis may be treated by angioplasty or a minor operation. In the absence of a stenosis, a low peak velocity (<45 cm/s) in the graft indicates proximal or distal disease progression and impending graft failure[22,23]. In 1986, the St. Mary's Hospital Radiology Department performed 406 angiograms in patients with infrainguinal grafts. In 1987, all grafts were examined by duplex scanning as well as angiography. Duplex scanning was shown to have a sensitivity of 100 per cent and a specificity of 96 per cent[22]. Since then, duplex scanning has been our method of choice for routine graft surveillance. In 1988, only 22 graft angiograms were performed, all to confirm a duplex scan finding of a stenosis of >50 per cent. This practice has kept the waiting list for angiography relatively short.

Detection of deep venous thrombosis

The use of duplex scanning is not limited to arterial disease. In the detection of deep venous thrombosis, the accuracy of duplex scanning is high. Comparison with venography has revealed a sensitivity and a specificity both close to 100 per cent above the calf[24,25], with a sensitivity of 70 per cent below the knee. In hospitals with a duplex scanning service, this is now the investigation of choice, and venography need rarely be performed in patients with suspected deep venous thrombosis.

Detection of venous insufficiency

With respect to varicose vein surgery, the anatomy of the popliteal fossa has been shown to be very variable, with only 56 per cent of saphenopopliteal junctions arising within 2–5 cm of the knee joint. In 30 per cent the short saphenous vein joins the deep system in the thigh or continues to the proximal long saphenous vein. The accuracy of a clinical examination at identifying the saphenopopliteal junction to within 2 cm is only 56 per cent, whereas the accuracy of duplex scanning to identify this junction to within 2 cm is 96 per cent. Thus a duplex scan to mark the site of the junction on the day of operation would eliminate the need for on-table venography (practised by some) and would provide every surgeon with the ability to position the skin incision accurately.

In the investigation of chronic venous disease, not only can duplex scanning be used to detect reflux in both superficial and deep veins, but it also makes quantification of reflux practical. Abnormal retrograde flow at peak reflux can vary from 2 to 40 ml/s. Reflux >10 ml/s is associated with a high incidence of venous ulceration irrespective of whether such reflux is in the deep or superficial system[26]. Colour flow imaging can provide a quick and accurate method of demonstrating and localizing sites of reflux from the deep to the superficial system (saphenofemoral and saphenopopliteal junctions) and is particularly useful in the localization of incompetent thigh and calf perforating veins[27].

Duplex scanning in abdominal ultrasonography

The duplex scan is not only a powerful diagnostic tool for the vascular surgeon; it has several other clinical applications. The recent introduction of probes that combine high resolution ultrasonography with Doppler at frequencies suitable for abdominal scanning has opened exciting new avenues. The intra-abdominal vessels can be identified both visually and by their flow signatures. Characteristic deviations from normal appearance are seen with stenosis. In addition, the ability to indicate direction of flow using Doppler techniques is helpful in evaluating portal vein haemodynamics. In portal hypertension, there is loss of the normal respiratory variation[28] and reversal of flow may be seen in the portal or splenic vein. Spontaneous portasystemic shunts may also be identified[29] and at present duplex scanning is the method of choice for checking portacaval shunt patency following surgery.

The mesenteric vasculature is also amenable to examination by duplex scanning. Each vessel has its own characteristic blood velocity pattern and change in flow can be detected following physiological stress (standard meal). This response is altered by pathological changes in the vessels. For instance, in health, blood flow in the superior mesenteric artery doubles following a standard meal; in the dumping syndrome this response is greatly exaggerated[30]. Many investigators now use duplex scanning as their first line investigation for superior mesenteric and coeliac trunk stenosis in patients with suspected mesenteric angina.

The detection of renal artery stenosis is difficult, time-consuming and requires a skilled operator; however, a sensitivity of 91 per cent and specificity of 95 per cent have been achieved[31,32]. Only 1 per cent of patients with hypertension have renal artery stenosis and a quick non-invasive screening technique is needed. Colour flow imaging should improve the ease with which this condition may be diagnosed.

In the field of transplantation medicine, duplex scanning has been used to monitor renal transplant parenchymal blood flow and renal artery velocity patterns. In acute rejection the renal vascular resistance increases, causing diastolic blood flow velocity to decrease and sometimes even to reverse[33]. This is an early indication of the onset of rejection. Improved diastolic flow may be detected in patients who respond to therapy. In hepatic transplantation, duplex scanning allows identification of the anatomy before operation. After operation, regular monitoring by duplex scanning allows early recognition of thrombosis of major vessels[34,35].

An exciting area of promise is in the identification of neoplastic growths. Neovascularization occurs in malignant tumours and its detection may aid diagnosis, characterize the tumour as slow growing or aggressive, and allow assessment of response to therapy. Liver tumours may sometimes be differentiated into haemangiomas, hepatomas and metastases on the basis of flow characteristics[36].

Duplex scanning in obstetrics

In obstetrics, ultrasonography has established its pre-eminence in antenatal diagnosis of anatomical defects. Duplex scanning, by its ability to detect blood velocity, offers the prospect of diagnosing physiological abnormalities. In the diagnosis of intrauterine growth retardation, the study of the blood flow velocity waveforms from the umbilical cord and the maternal uterine arteries has enabled obstetricians to detect early placental insufficiency by non-invasive means[37,38].

Cost-effectiveness of duplex scanning

As a non-invasive technique, duplex scanning is particularly suited to repeated examinations and may be used for both diagnosis and follow-up; often the alternative is an invasive procedure. Despite this, many vascular surgeons do not have access to the facility; some argue that such equipment is for teaching hospitals only. However, in 1991 the argument that the cost of a duplex scanner can only be justified in major centres is no longer tenable. The actual number of patients saved from a radiological procedure in our department is: 90 per cent of patients with suspected deep venous thrombosis, 90 per cent of patients with suspected post-thrombotic limb, 80 per cent of patients with femorodistal bypass grafts, and 70 per cent of patients with suspected carotid bifurcation disease.

The cost of non-ionic contrast agent and disposables for a venogram or intravenous digital subtraction angiography is approximately £120. The annual cost of a duplex scanning service is £43 000 (cost of equipment £60 000 repaid over 5 years, annual service contract £6000, senior ultrasonographer with medical supervision £25 000 per annum). These costs could be recouped by approximately 360 duplex scans, solely from the contrast agent and disposables saved. Additional scans would constitute a substantial saving on the hospital budget. A duplex scanner in full use (four scans per session) providing 2000 scans per year might save the Radiology Department as much as £192 000 solely on contrast agent and disposables; it might allow up to 1600 invasive investigations to be replaced by non-invasive studies.

The future

Over the past 15 years, the emphasis in duplex scanning has been on detection of abnormal flow patterns, and the B-mode image has largely been ignored. This is because the resolution of the ultrasonic image of the early duplex machines was poor, enabling accurate placement of a Doppler sample volume but not itself contributing information about the nature of the arterial wall. However, there has been a steady improvement in image quality, and attempts have been made to identify morphological features of vessel wall plaques[39–41].

The development of high resolution ultrasonography (resolution to 0·2 mm) has enabled the identification of details of the arterial wall even before plaque formation. Pignoli[42] has shown that ultrasonically-visualized arterial wall layers correlate with histological layers; the first echogenic and echolucent lines indicate intima and media, and the second echogenic line, adventitia. Poli *et al.*[43] have shown that change in the intima–media thickness occurs in hypercholesterolaemia, and Salonen and Salonen[44] and Salonen *et al.*[45] have followed a population of middle-aged men and shown that it is possible to monitor the progression of arterial wall changes by measuring the intima–media thickness, and that the strongest predictors of progression were age, smoking habit, low density lipoprotein cholesterol, leucocyte count and platelet aggregability. Epidemiological studies have begun to use this measurement in long-term studies. One such study[46] found that patients with an increased arterial wall intima–media thickness at entry had significantly increased levels of total serum cholesterol, low density lipoprotein cholesterol, triglycerides and systolic blood pressures compared with controls.

Identification of arterial wall abnormalities by ultrasonography has already been shown to correlate with the presence of cardiovascular risk factors[47]. Qualitative changes in the ultrasonogram appearance of the artery wall have been studied by Belcaro *et al.*[48] and have been seen to correlate with the risk of development of symptomatic disease in normal volunteers followed up for 3 years. Intima–media thickness measurements can be made validly and reproducibly within the common carotid, carotid bifurcation and internal carotid arteries, and these are now being used to monitor the development of atherosclerosis in large multicentre studies in the USA[46] and Italy.

High resolution ultrasonography is at present limited to the superficial arteries, in particular to the carotid and femoral arteries, but as a screening test for the presence of general atherosclerotic disease this seems to be sufficient[48].

Conclusion

Over the past 15 years duplex ultrasonography has developed into a powerful clinical and investigative tool. Its applications are diverse, and this review is by no means exhaustive. A duplex scan should no longer be regarded as an added extra but rather as the mainstay of vascular diagnosis and follow-up. Angiography should be reserved for use in complicated cases and as a preliminary to intervention. This policy would not only reduce the number of patients exposed to the risk of an invasive procedure but also produce savings to the hospital budget, an important consideration in the present times of austerity.

Like angiography and other exacting modern investigations, duplex ultrasonography is operator-dependent. Thus, adequate training of the operator of a duplex scanner, although easier than training a radiologist, is essential. As has been outlined in this review, duplex scanning is not limited to the diagnosis of peripheral vascular disease; it is a tool of wide-ranging abilities. A district general hospital with a vascular practice can no longer justify being without one.

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References

1. Burns RW. Doppler ultrasonic arteriography. In: Bernstein EF, ed. *Non Invasive Techniques in Vascular Disease*. St. Louis: CV Mosby, 1985: 212–17.
2. Bernstein EF, Dilley RB, Goldberger LE, Gosink BB, Leopold GR. Growth rates of small aortic aneurysms. *Surgery* 1976; **8**: 765–70.
3. Barber F, Baker D, Nation A *et al.* Ultrasonic duplex echo-Doppler scanner. *IEEE Trans Biomed Eng* 1974; **21**: 109–13.
4. Breslau PJ, Fell G, Phillips DJ, Thiele BL, Strandness DE Jr. Evaluation of carotid bifurcation disease: the role of common carotid artery velocity patterns. *Arch Surg* 1982; **117**: 58–60.
5. Persson AV. Use of ultrasonic colour imaging in the evaluation of the venous system. In: Salmasi AM, Nicolaides AN, eds. *Cardiovascular Applications of Doppler Ultrasound*. London: Churchill Livingstone, 1989: 355–64.
6. Roederer GO, Strandness DE Jr. A simple spectral parameter for the classification of severe carotid disease. *Bruit* 1984; **8**: 174–8.
7. Williams MA, Deacon DFS, Szendro G, Belcaro G, Nicolaides AN. Duplex scanning in the detection and grading of internal carotid artery stenosis: improved criteria. In: Salmasi AM, Nicolaides AN, eds. *Cardiovascular Applications of Doppler Ultrasound*. London: Churchill Livingstone, 1989: 247–60.
8. Reilly LM, Lusby RJ, Hughes L, Ferrell LD, Stoney RJ, Ehrenfeld WK. Carotid plaque histology using real time ultrasonography. Clinical and therapeutic implications. *Am J Surg* 1983; **146**: 188–93.
9. Bluth EI, Kay D, Merritt CRB *et al.* Sonographic characterisation of carotid plaque: detection of haemorrhage. *AJR* 1986; **146**: 1061–5.
10. Chambers BR, Norris JW. Outcome in patients with asymptomatic neck bruits. *N Engl J Med* 1986; **315**: 860–5.
11. Hennerici M, Hulsbomer H-B, Hefter H, Lammers D, Rautenberg W. Natural history of asymptomatic extracranial arterial disease: results of a long term prospective study. *Brain* 1987; **110**: 777–91.
12. Roederer GO, Langois YE, Lusiani L *et al.* Natural history of carotid artery disease on the side contralateral to endarterectomy. *J Vasc Surg* 1984; **1**: 62–72.
13. Boggousslavsky J, Despland P-A, Regli F. Asymptomatic tight stenosis of the internal carotid artery: long term prognosis. *Neurology* 1986; **36**: 861–3.
14. Moneta GL, Taylor DC, Zieler RE, Kazmers A, Beach K, Strandness DE Jr. Asymptomatic high-grade internal carotid

stenosis: is stratification according to risk factors or duplex spectral analysis possible. *J Vasc Surg* 1989; **10**: 475–83.

15. Visona A, Lusiani L, Castellani V *et al.* The echo-Doppler (duplex) system for the detection of vertebral occlusive disease: comparison with angiography. *J Ultrasound Med* 1986; **5**: 247–50.
16. Ackerstaff RGA, Eikleboom BC, Hoeneveld H, Moll FL, Vries AR. Ultrasonic duplex scanning in atherosclerotic disease of the innominate, subclavian and vertebral arteries. A comparative study with angiography. *Ultrasound Med Biol* 1984; **10**: 409–18.
17. Legemate DA, Teeuwen C, Hoeneveld H, Ackerstaff RGA, Eikelboom BC. The potential of duplex scanning to replace aorto-iliac and femoro-popliteal angiography. *Eur J Vasc Surg* 1989; **3**: 49–54.
18. Cossman DV, Ellison JE, Wagner WH *et al.* Comparison of contrast arteriography to arterial mapping with colour-flow duplex imaging in the lower extremities. *J Vasc Surg* 1989; **10**: 522–9.
19. Bagi P, Schroeder T, Sillesen H, Lorentzen JE. Real time B-mode mapping of the great saphenous vein. *Eur J Vasc Surg* 1989; **3**: 103–5.
20. Bandyk DF, Moldenhaurer P, Lipchik E *et al.* Accuracy of duplex scanning in the detection of stenosis after carotid endarterectomy. *J Vasc Surg* 1988; **8**: 696–702.
21. Cata R, Seabrook GR, Bandyk DF *et al.* Intraoperative duplex scanning following carotid artery reconstruction. *J Vasc Surg* 1989; **13**: 31–6.
22. Grigg MJ, Wolfe JHN, Tovar A, Nicolaides AN. The reliability of duplex derived haemodynamic measurements in the assessment of femoro-distal grafts. *Eur J Vasc Surg* 1988; **2**: 171–81.
23. Bandyk DF, Seabrook GR, Moldenhauer P *et al.* Haemodynamics of graft stenosis. *J Vasc Surg* 1988; **8**: 688–95.
24. Hannan LA, Stedje KJ, Skorcz MJ *et al.* Venous imaging of the extremities: our first twenty-five hundred cases. *Bruit* 1986; **10**: 29–32.
25. Semrow CM, Freidell M, Buchbinder D *et al.* Characterisation of lower extremity venous disease using real time B-mode ultrasonic imaging. *J Vasc Technol* 1987; **11**: 187–91.
26. Vasdekis S. Doppler ultrasound in chronic venous insufficiency. In: Salmasi AM, Nicolaides AN, eds. *Cardiovascular Applications of Doppler Ultrasound.* London: Churchill Livingstone, 1989: 323–32.
27. Nicolaides A, Christpoulos D, Vasdekis S. Progress in the investigation of chronic venous insufficiency. *Ann Vasc Surg* 1989; **3**: 278–92.
28. Bolondi L, Gandolfi L, Arienti V *et al.* Ultrasonography in the diagnosis of portal hypertension: diminished response of the portal vessels to respiration. *Radiology* 1982; **142**: 167–72.
29. Di Candio G, Campatelli A, Mosca F, Santi V, Casanova P, Bolondi L. Ultrasound detection of unusual spontaneous portosystemic shunts associated with uncomplicated portal hypertension. *J Ultrasound Med* 1985; **4**: 297–305.
30. Qamar MI, Reed AE, Skidmore R, Evans JM, Wells PNT. Transcutaneous Doppler ultrasound measurement of superior mesenteric artery blood flow in man. *Gut* 1986; **27**: 100–5.
31. Norris CS, Pfeiffer JS, Rittgers SE, Barnes RW. Non-invasive evaluation of renal artery stenosis and renovascular resistance: experimental and clinical studies. *J Vasc Surg* 1984; **1**: 192–201.
32. Kohler TR, Zierler RE, Martein RL *et al.* Non-invasive diagnosis of renal artery stenosis by ultrasonic duplex scanning. *J Vasc Surg* 1986; **4**: 450–6.
33. Rigsby CM, Burns PN, Weltin GG, Chen B, Bia M, Taylor KJ. Doppler signal quantification in renal allografts: comparison in normal and rejecting transplants with pathological correlation. *Radiology* 1987; **162**: 39–42.
34. Letourneau JG, Day DI, Ascher NL. Abdominal ultrasonography after hepatic transplantation: results in 36 patients. *AJR* 1987; **149**: 299–303.
35. Wozney P, Zajko AB, Bron KM *et al.* Vascular complications after liver transplantation, a five year experience. *AJR* 1986; **147**: 657–63.
36. Taylor KJW, Ramos I, Morse SS *et al.* Focal liver masses: differential diagnosis with pulsed Doppler US. *Radiology* 1987; **164**: 643–7.
37. Trudinger BJ, Giles WB, Cook CM. Utero-placental blood flow velocity time waveforms in normal and complicated pregnancy. *Br J Obstet Gynaecol* 1985; **92**: 39–45.
38. Gill RW, Kossoff G, Warren PS, Garrett WJ. Umbilical venous flow in normal and complicated pregnancy. *Ultrasound Med Biol* 1984; **10**: 349–63.
39. Johnson JM, Konnelly MM, Decesare D *et al.* Natural history of asymptomatic carotid plaque. *Arch Surg* 1985; **120**: 1010–12.
40. Gray-Weale AC, Graham J, Burnett JR, Byrne K, Lusby RJ. Carotid artery atheroma. Comparison of preoperative B-mode ultrasound appearance with carotid endarterectomy specimen pathology. *J Cardiovasc Surg* 1988; **29**: 676–81.
41. Langsfield M, Gray-Weale AC, Lusby RJ. The role of plaque morphology and diameter reduction in the development of new symptoms in asymptomatic carotid arteries. *J Vasc Surg* 1989; **9**: 548–57.
42. Pignoli P. Ultrasound B-mode imaging for arterial wall thickness measurement. *Atherosclerosis Rev* 1984; **12**: 177–84.
43. Poli A, Tremoli E, Colombo A *et al.* Ultrasonographic measurement of the common carotid wall thickness in hypercholesterolaemic patients. *Atherosclerosis* 1988; **70**: 253–61.
44. Salonen R, Salonen JT. Progression of carotid atherosclerosis and its determinants: a population based ultrasonography study. *Atherosclerosis* 1990; **81**: 33–40.
45. Salonen JT, Salonen R, Seppanen K *et al.* Interactions of serum copper, selenium, and low density lipoprotein cholesterol in atherogenesis. *Br Med J* 1991; **302**: 756–60.
46. The ARIC Investigators. The atherosclerosis risk in communities (ARIC study) design and objectives. *Am J Epid* 1989; **129**: 687–92.
47. Scheinberg P. Controversies in the management of cerebrovascular disease. *Neurology* 1988; **38**: 1609–16.
48. Belcaro G, Nicolaides AN, Renton S *et al.* Arterial ultrasonic biopsy to evaluate the cardiovascular system. A noninvasive technique to screen for cardiovascular disease and to evaluate regression and progression of arteriosclerosis: a preliminary report. *Curr Ther Res* 1990; **48**: 116–27.

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Microcirculatory and trophic effects of short chain fatty acids in the human rectum after Hartmann's procedure

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Short chain fatty acids (acetic, propionic and butyric) were instilled into the rectum of patients who had undergone Hartmann's procedure. The following parameters were examined before and after a 2-week treatment period with short chain fatty acids (100 ml twice daily at a total concentration of 150 mM): (1) microcirculatory effects in vivo *using a laser Doppler flow technique, and (2) morphometrical changes in mucosal biopsies. The following parameters were significantly increased in all patients after treatment: (1) mucosal blood flow, (2) the fractional crypt cell epithelium plus surface epithelium volume in relation to total tissue volume down to the muscularis mucosa, (3) nuclear volume in the crypt and the surface epithelium, and (4) the fractional nuclear volume to total cell volume in the crypt and the surface epithelium. These data suggest that short chain fatty acids in the human colon have trophic and vasodilatory effects.*

Short chain fatty acids are predominantly produced in the large bowel of non-ruminant mammals by bacterial, anaerobic fermentation of carbohydrates[1]. Acetic, propionic and butyric acids are generated in a nearly constant molar ratio of 60:25:15 and account for approximately 83 per cent of all short chain fatty acids produced[2,3]. Studies of colonocytes have shown that these compounds provide the mucosa with its preferred oxidative fuel[4–6].

There are several indications of trophic effects of short chain fatty acids in the colon. Their presence in the lumen of the rat colon stimulates mucosal cell proliferation[7–9]. Fibre-free enteral diets induce atrophy in the rat colon as does total parenteral nutrition[10–12]. These changes probably result from the decreased production of short chain fatty acids from carbohydrate fibres that would normally reach the colon.

Short chain fatty acids may also have direct circulatory effects in the colon. The compounds, alone and in combination, dilate isolated resistance arteries from the human colon in a concentration-dependent manner[13] and may stimulate the microcirculation in the colonic wall under *in vivo* conditions.

In man, Hartmann's procedure results in a closed rectum deprived of its natural short chain fatty acid source. Theoretically, this may induce atrophy of the bowel wall and a decrease in mucosal blood flow. The rectum in these patients could be a suitable model for the examination of the importance of short chain fatty acids under *in vivo* conditions. The purpose of this study was to examine possible microcirculatory and morphometrical changes in response to instillation of short chain fatty acids into the rectum of patients undergoing Hartmann's procedure.

Patients and methods

Patients and treatment

Six patients, aged 57–74 years (two men), who had undergone Hartmann's procedure for perforated diverticulitis were included in the study. Colon continuity was restored after a period of 4–11 months. For a period of 10–14 days before restoration of bowel continuity, 100 ml short chain fatty acids (150 mM) in the proportion described by Sakata and Engelhardt[14] were instilled into the rectum twice daily. Mucosal blood flow was determined by a laser Doppler flow technique and mucosal biopsies (approximately 3 × 3 × 3 mm) were taken before and after treatment.

The protocol of the study conformed with the Declaration of Helsinki II and was approved by the Aarhus County Ethics Committee.

Because of the limited number of suitable patients, the effects of placebo treatment could not be tested but the patients served as their own controls and the investigator was blind with respect to patient identity and whether short chain fatty acid instillation had occurred.

Mucosal blood flow

Rectal mucosal blood flow was measured by a laser Doppler flow technique with a differential detector system (Periflux, Perimed, Stockholm, Sweden)[15,16]. After calibration, a probe was placed on the rectal mucosa through a proctoscope. The probe was placed gently on the bulging mucosa, care being taken not to interfere with mucosal circulation. Measurements were made on the anterior and the posterior wall approximately 10 cm from linea dentata. A minimum of 4 h had elapsed between the last instillation of short chain fatty acids and the measurements. The person who performed the proctoscopy and placed the laser Doppler flow probe was blind with respect to the actual flow recordings.

Histological specimens

Two biopsies were taken from the anterior rectal wall through a proctoscope approximately 10 cm from linea dentata, before and after a 10–14-day treatment period. Biopsies were embedded in paraffin and cut in 3 μm thick sections. One biopsy was cut vertically with respect to the surface mucosa. In the other, isotropic sections were made by the method of Mattfeldt *et al.*[17]. Vertical sections were used to estimate the volume of the epithelium as a fraction of the total volume of tissue down to the muscularis mucosa. Isotropic sections were used to determine the nuclear volume in relation to total cell volume and to estimate the volume-weighted mean nuclear volume v_v[18] in the surface and in the crypt epithelium.

Stereological estimations

The principles have been described earlier in detail[19,20]. A monocular Olympus BHS-2 microscope (Tokyo, Japan) equipped with a simple mirror and a × 100 oil-immersion lens was used. The fields of vision were projected to a final magnification × 1650. In each histological section, four fields of vision were investigated and chosen at random without overlap. The relative volume of epithelium (vertical sections) was determined by projecting the fields of vision on to a spatial grid. By counting the points hitting the different structures, an estimate of the relative volumes was obtained[21].

The stereological estimation of the volume-weighted mean nuclear volume, v_v (isotropic sections) was made by projecting the fields of vision on to an orientation frame. A transparent grid with test points

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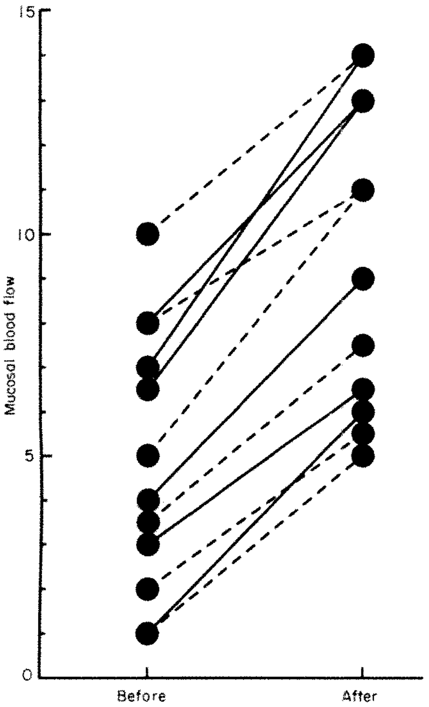

Figure 1 *Relative mucosal blood flow (arbitrary units) before and after a 10–14-day period with short chain fatty acid instillation into the human rectum.* ●- - -●, *Measurements from the anterior wall;* ●——●, *from the posterior wall. All patients showed an increase in mucosal blood flow, both on the anterior and the posterior wall*

associated with lines was superimposed on to the orientation frame. A random number between 1 and 97 was selected and determined the starting orientation. For each subsequent measurement, a constant number ($n = 37$) was added to the initial orientation number. The directions of the test lines were thereby weighted as a function of their angles with the vertical axis of the section. Linear intercepts through nuclei were measured with an ordinary ruler in the direction dictated by the test lines. By multiplying the averaged, cubed mean intercept length, l^3, by $\pi/3$, an unbiased estimate of the three-dimensional, volume-weighted mean nuclear volume, nuclear v_v, was obtained[18].

The fractional nuclear volume in relation to total cell volume (isotropic sections) was determined by projecting the fields of vision on to a spatial grid as described earlier.

Composition of the treatment

The solution contained in mM: sodium acetate 75·0, sodium propionate 43·8, sodium butyrate 31·3; and parahydroxybenzoatdiluendum 10 per cent (DAK laboratoriet, Copenhagen, Denmark). The pH of the solution was 7·0.

Statistics

Statistical differences between two means were determined by Wilcoxon's test for paired differences, $P < 0·05$ representing the level of significance. Unless smaller than the symbols, the s.e.m. are expressed as error bars in the figures.

Results

This study showed a significant increase in mucosal blood flow, ranging from a 1·5-fold increase to a five-fold increase, highest for the patients with the lowest starting values (*Figure 1*).

The epithelial volume (crypt plus surface) as a fraction of the total volume down to the muscularis mucosa increased significantly during the period of short chain fatty acid instillation (*Figure 2*). The increase ranged from 28 to 45 per cent. All six patients showed an increase in nuclear volume as a fraction of total cell volume. The increase ranged from 7 to 31 per cent and from 3 to 9 per cent (*Figure 3*) in crypt and surface epithelium, respectively ($P < 0·05$). The volume-weighted mean nuclear volume v_v was increased in all six patients during the period of short chain fatty acid instillation. The enlargement ranged from 32 μm^3 to 135 μm^3 and from 22 μm^3 to 90 μm^3 (*Figure 4*) in crypt and surface epithelium, respectively ($P < 0·05$).

Discussion

The present *in vivo* study demonstrates trophic changes in the human colon after short chain fatty acid instillation. One explanation for the significant increase in the fraction crypt cell epithelium plus surface epithelium volume in relation to total tissue volume down to the muscularis mucosa could be a decrease in the volume of the interstitial tissue. Infusion of short chain fatty acids into the colon of rats, however, has been shown to enhance the healing of colonic anastomoses[22]. An important process occurred in the interstitium, indicated by a significantly elevated proline content in the anastomosis in the group receiving short chain fatty acids compared with the placebo-treated group. It therefore seems unlikely that short chain fatty acids stimulate interstial growth in rats while inducing atrophy in humans. The most likely explanation for the observation in the present study is simultaneous growth of mucosal and interstitial cells. Growth of mucosal cells apparently exceeded that of interstitial cells, in agreement with animal studies showing a stimulatory effect of short chain fatty acids under *in vivo* conditions on the colonic mucosa[7–9].

Studies involving rats have shown that DNA, RNA and protein content are increased in the colonic mucosa after short chain fatty acids instillation[9]. The present study showed an absolute increase in the mean nuclear volume, in the crypt and in the surface epithelium and is in accord with these observations. An increase in nuclear volume, other things being equal, suggests an increase in nuclear DNA, RNA and protein content reflecting an increased synthetic activity. An increase in the cell synthetic activity, however, would also be expected to induce an increase in the cytoplasmic volume. The increase in the nuclear to cytoplasmic ratio observed in this study could be explained by an increase at both sites, with nuclear exceeding cytoplasmic growth.

The laser Doppler flow recordings demonstrated an increase in mucosal blood flow, being greatest from a low initial value.

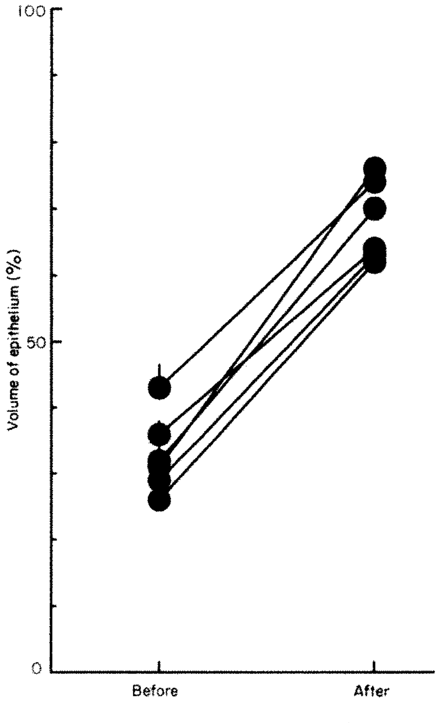

Figure 2 *Crypt epithelium volume plus the surface epithelium volume as a fraction of the total tissue volume down to the muscularis mucosa before and after instillation of short chain fatty acids*

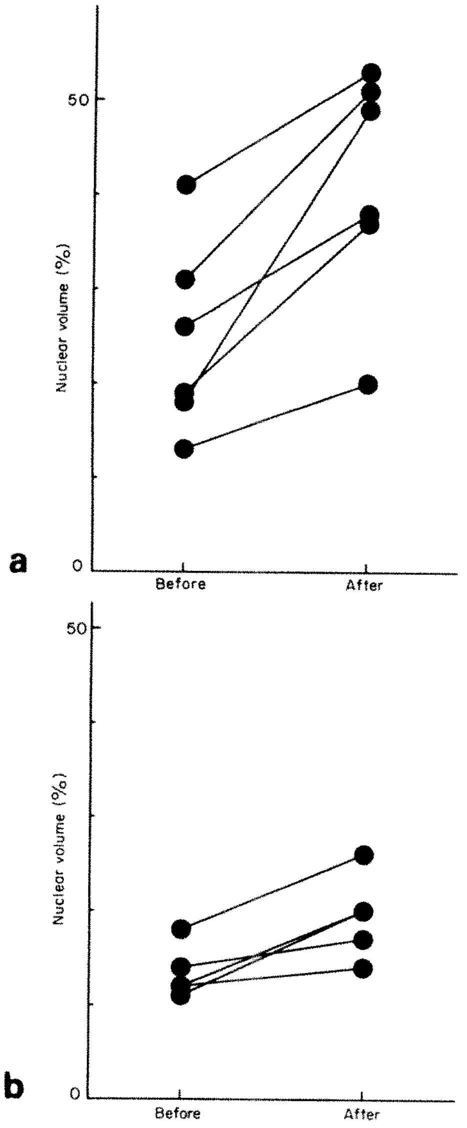

Figure 3 *Nuclear volume in relation to the total cell volume in* **a** *crypt and* **b** *surface epithelium, before and after instillation of short chain fatty acids*

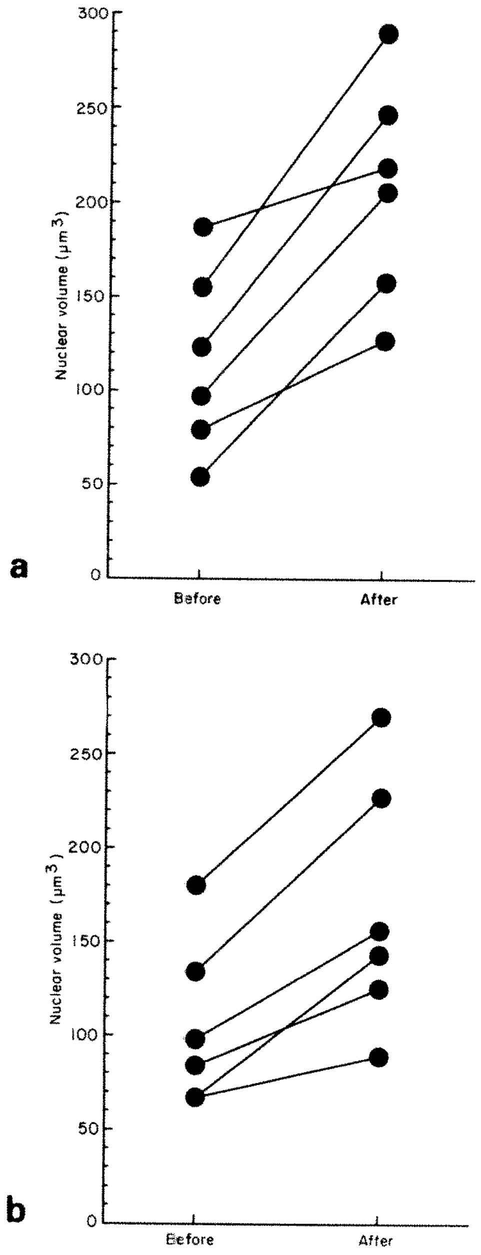

Figure 4 *Volume-weighted mean nuclear volume* v_v *in* **a** *crypt and* **b** *surface epithelium, before and after short chain fatty acid instillation*

We have shown that all three short chain fatty acids, alone and in combination, dilate isolated human colonic resistance arteries in a concentration-dependent manner[13]. A likely explanation for the increase in mucosal blood flow in this study is stimulation of the microcirculation by a direct action on the resistance arteries, the main regulators of the blood flow to an organ. Another explanation could be an increased blood flow secondary to an increased metabolism, in the sense that short chain fatty acids are the preferred oxidative fuel for the colonic mucosa. A third explanation is that the short chain fatty acids stimulate angiogenesis in the atrophic rectum to increase the total number of capillaries.

Instillation of short chain fatty acids into the colon is a simple, cheap and safe procedure to achieve a local effect because any absorbed short chain fatty acids are quickly cleared by the liver[23,24]. Instillation of short chain fatty acids after low anterior resections for carcinoma may be an indication for short chain fatty acid therapy; attempting to reduce radiological and clinical leakage through the anastomosis. The frequency of clinical leakage is 2–18 per cent[25,26], and radiological leakage 6–35 per cent[27,28]. Gruber suggested that microcirculatory failure is the main factor determining leakage[29]. From a therapeutic point of view, therefore, a good and more controlled way to obtain an increased microcirculatory flow to the resection edges could be by postoperative instillation of short chain fatty acids.

Acknowledgements

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References

1. Cummings JH, Branch WJ. Fermentation and the production of short chain fatty acids in the human large intestine. In: Vahouny GB, Kritchevsky D, eds. *Dietary Fiber. Basic and Clinical Aspects.* New York: Plenum Press, 1986: 131–52.
2. Miller TL, Wolin MJ. Fermentations by saccharolytic intestinal bacteria. *Am J Clin Nutr* 1976; **32**: 164–72.
3. Nyman M, Asp NG. Fermentation of dietary fibre components in rat intestinal tract. *Br J Nutr* 1982; **47**: 357–66.
4. Roediger WEW. Role of anaerobic bacteria in the metabolic welfare of the colonic mucosa in man. *Gut* 1980; **21**: 793–8.
5. Roediger WEW. Utilization of nutrients by isolated epithelial cells of the rat colon. *Gastroenterology* 1982; **83**: 424–9.

6. Ardawi MSM, Newsholme EA. Fuel utilization in colonocytes of the rat. *Biochem J* 1985; **231**: 713–19.
7. Sakata T, Engelhardt WV. Stimulatory effect of short chain fatty acids on the epithelial cell proliferation in rat large intestine. *Comp Biochem Physiol* 1983; **74A**: 459–62.
8. Sakata T. Stimulatory effect of short chain fatty acids on epithelial cell proliferation in the rat intestine. *Br J Nutr* 1987; **M58**: 95–103.
9. Kripke KA, Fox AD, Berman JM *et al.* Stimulation of intestinal mucosal growth with intracolonic infusion of short chain fatty acids. *J Parenter Enteral Nutr* 1989; **13**: 109–16.
10. Janne P, Carpentier Y, Willems G. Colonic mucosal atrophy induced by a liquid diet in rats. *Am J Dig Dis* 1980; **22**: 808–12.
11. Ryan GP, Dudrick SJ, Copeland EM *et al.* Effect of various diets on colonic growth in rats. *Gastroenterology* 1979; **77**: 658–63.
12. Sircar B, Johnson LR, Licthenberger LM. Effect of synthetic diets on gastrointestinal mucosa DNA synthesis in rats. *Am J Physiol* 1983; **244**: G327–35.
13. Mortensen FV, Nielsen H, Mulvany MJ, Hessov I. Short chain fatty acids dilate isolated human colonic resistance arteries. *Gut* 1990; **31**: 1391–4.
14. Sakata T, Engelhardt WV. Stimulatory effect of short chain fatty acids on the epithelial cell proliferation in rat large intestine. *Comp Biochem Physiol* 1983; **73A**: 459–62.
15. Ahn H, Lindhagen J, Lundgren O. Measurement of colonic blood flow with laser Doppler flowmetry. *Scand J Gastroenterol* 1986; **21**: 871–80.
16. Ahn H, Johansson K, Lundgren O, Nilsson GE. *In vivo* evaluation of signal processors for laser Doppler tissue flowmeters. *Med Biol Eng Comput* 1987; **25**: 207–11.
17. Mattfeldt T, Mall G, Gharehbaghi H, Möller P. Estimation of surface area and length with the orientator. *J Microsc* 1989; **159**: 301–17.
18. Sørensen FB. Stereological estimation of mean and variance of nuclear volume from vertical sections. *J Microsc* 1991; (in press).
19. Gundersen HJG, Bendtsen F, Korbo L *et al.* Some new, simple and efficient stereological methods and their use in pathological research and diagnosis. *APMIS* 1988; **96**: 379–94.
20. Gundersen HJG, Bagger P, Bendtsen TF *et al.* The new stereological tools: disector, fractionator, nucleator and point sampled intercepts and their use in pathological research and diagnosis. *APMIS* 1988; **96**: 857–81.
21. Weibel ER. *Stereological Methods for Biological Morphometry.* Vol 1. New York: Academic Press, 1979; 28–100.
22. Rolandelli R, Koruda MJ, Settle RG *et al.* Effects of intraluminal infusion of short chain fatty acids on the healing of colonic anastmosis in the rat. *Surgery* 1986; **100**: 198–200.
23. Buckley BM, Williamson DH. Origins of blood acetate in the rat. *Biochem J* 1977; **166**: 539–45.
24. Herrmann DBJ, Herz R, Frolich J. Role of gastrointestinal tract and liver in acetate metabolism in humans and rats. *Eur J Clin Invest* 1985; **15**: 221–6.
25. Goligher JC, Lee PWG, Simpkins KC, Limbolt DJ. A controlled comparison of one- and two-layer technique of suture for high and low colorectal anastomosis. *Br J Surg* 1977; **64**: 609–14.
26. Goligher JC, Lee PWG, Mactie J, Simpkins KC, Lintoot DJ. Experience with the Russian model 249 suture gun for anastomosis of the rectum. *Surg Gynecol Obstet* 1979; **148**: 517–24.
27. Leicester RJ, Heald RJ. Towards fewer colostomies – the impact of circular stapling devices on the surgery of rectal cancer. *Br J Surg* 1980; **67**: 198–200.
28. Matheson NA, Irving AD. Single layer anastomoses after rectosigmoid resection. *Br J Surg* 1975; **62**: 239–42.
29. Gruber UF. Volume expansion and flow promotion in shock. *Postgrad Med J* 1969; **45**: 534–38.

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Anti-epithelial membrane antigen monoclonal antibodies and radioimmunolocalization of colorectal cancer

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The monoclonal antibodies LICR-LON M8 and 77-1, which react with epithelial membrane antigen, showed a strong reaction with colorectal cancer on immunohistochemistry. In a radioimmunolocalization study in patients with colorectal cancer, ^{111}In-labelled M8 detected 13 of 16 tumour sites present in 16 patients. ^{111}In-labelled 77-1 detected 10 of 15 tumour sites present in 14 patients. The high radioactive background in the liver prevented the detection of hepatic metastases in eight patients (five in the M8 and three in the 77-1 group). The mean(s.d.) tumour to normal colon ratio was 2·5(1·2) for M8 and 1·6(0·5) for 77-1 at day 6 after antibody administration. The mean(s.d.) tumour to blood ratio was 4·9(3·7) for M8 and 3·6(1·5) for 77-1. There was no statistical difference between these results. All scan-positive cancers reacted with M8 and 77-1 on immunohistochemistry. The results suggest that these monoclonal antibodies may have a role in the immunolocalization of colorectal cancer.

Localization of colorectal tumours using radiolabelled tumour-associated antibodies was successfully carried out by Goldenberg and associates some 10 years ago using a polyclonal sheep antiserum to carcinoembryonic antigen (CEA)[1]. Hybridoma technology allows large amounts of pure and identical monoclonal antibodies to be produced[2]. Many monoclonal antibodies have been raised to CEA, but other antibodies recognizing tumour cell surface antigens have been successfully used for the radioimmunolocalization of colorectal tumours, including[3,4] 19-9 and 17-1A. The antibodies do not appear to be tumour-specific, but react with antigens which are expressed in larger quantities by tumour tissue. Antibody reactivity with more than one tumour type is common; monoclonal antibody (MAb) B72.3 was raised to breast cancer but localizes to colorectal cancer[5], and MAb 791T/36 was raised to an osteogenic sarcoma but produces images of bone[6] and colonic tumours[7].

Tumour heterogeneity[8], the human anti-mouse antibody response[9] and lack of colorectal cancer-specific monoclonal antibodies demonstrate the need for monoclonal antibodies with strong reactivity to colorectal cancer. In an immunoperoxidase study, 25 monoclonal antibodies were screened for reactivity to colorectal cancer[10]. Two monoclonal antibodies[11,12], LICR-LON M8 (M8) and 77-1, were found to have a strong preferential reactivity with colorectal cancer compared with normal colon[10]. Both monoclonal antibodies[13,12] recognized epitopes of epithelial membrane antigen (EMA)[14,15], which is expressed by most epithelial tumours, including colorectal cancer[16]. M8 has been used in the immunolocalization of metastastic breast carcinoma[17]. A localization study with ^{125}I- and ^{111}In-radiolabelled antibody 77-1 has shown[18] that it localizes to an EMA-expressing renal xenograft XK1. On this basis, ^{111}In-labelled M8 and 77-1 were selected for localization studies in patients with colorectal cancer.

Patients and methods

Approval for the study was obtained from the ethics committee of University College Hospital, and patients with colorectal cancer were invited to take part. A fully informed verbal and written consent was obtained. Patients with renal or hepatic disease or a history of atopy were excluded. An intradermal injection of the antibody was given to test for an allergic reaction. Sixteen patients took part in the radiolabelled M8 localization study (*Table 1*). Fourteen patients took part in the 77-1 localization study (*Table 2*).

Preparation of antibody

M8, a monoclonal antibody of immunoglobulin (Ig) G_1 subclass, was raised against human milk fat globule membrane[11]. A second monoclonal antibody, 77-1, of IgG_{2a} subclass, was raised against a membrane extract from human bladder carcinoma[12]. Antibodies for the clinical study were produced in BALB/c mice as ascitic fluid and purified using a column of staphylococcal protein-A (Pharmacia Fine Chemicals, Milton Keynes, UK) and conjugated with the tricyclic anhydride of diethylenepenta-acetic acid (DTPA) (Sigma, Poole, UK) at molar ratios of 2:1 as previously described[18,19]. The antibody–DTPA conjugates were sterilized by ultrafiltration using a Millipore 0·22 μm filter (Millipore SA, Molsheim, France) and tested for pyrogenicity (Safepharm, Derby, UK).

Labelling with ^{111}In

Approximately 700–1000 μg antibody–DTPA conjugate was added to 148 MBq indium-111 chloride (INSIP, Amersham International, Amersham, UK) for 20 min. It was then passed through a G25 Sephadex column (Pharmacia Fine Chemicals) which had been saturated with human serum albumin in glycine solution (pH 3·5). The

Table 1 *Details of patients administered with ^{111}In-labelled M8*

Patient	Sex	Age	Site	Liver metastases
1	F	50	Caecum	
2	F	52	Sigmoid	
3	F	71	Rectosigmoid	
4	M	53	Rectosigmoid	
5	M	69	Rectum	
6	M	84	Caecum	
7	M	77	Rectum	
8	M	83	Rectum	Present
9	F	71	Rectosigmoid	
10	F	82	Rectosigmoid	Present
11	M	74	Rectum	
12	F	72	Hepatic flexure	
13	M	63	Rectosigmoid	Present
14	M	63	Recurrent sigmoid	Present
15	F	71	Recurrent rectum	Present
16	F	62	Recurrent rectum	

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Table 2 *Details of patients administered with* ^{111}*In-labelled 77-1*

Patient	Sex	Age	Site	Liver metastases
1	F	72	Sigmoid	
2	F	79	Rectum	
3	M	59	Rectum	
4	M	69	Sigmoid	
5	F	75	Sigmoid	
6	M	52	Rectum	
7	F	66	Caecum	
8	F	92	Caecum/sigmoid	Present
9	M	85	Sigmoid	
10	M	70	Sigmoid	Present
11	F	77	Rectum	Present
12	M	74	Rectum	
13	M	66	Recurrent sigmoid	
14	F	84	Recurrent rectum	

labelled antibody was eluted with 10 ml glycine (pH 3·5), and 1 ml aliquots were collected and counted for the identification of the labelled antibody, which was usually in fractions five and six. The immunoreactivity of the radiolabelled antibodies was tested by means of a cell binding assay[18] with the target cell MCF7.

Administration of radiolabelled antibody and γ camera scanning

An intradermal test dose of 10 μg/0·2 ml was given to test for sensitivity and followed 20 min later with a slow intravenous injection of radiolabelled antibody (500 μg, total activity 80 MBq). Images were obtained using the Siemens 37 ZLC LFOV (Siemens PLC, Sunbury-on-Thames, Middlesex, UK) γ camera with a 280 keV medium-energy parallel-hole collimator, and information was stored on the Nodecrest Micas 1000 computer (Nodecrest, Byfleet, UK). Anterior and posterior views were obtained of the abdomen and pelvis, and an outlet view with the patient sitting on the face of the camera was acquired. The first three patients administered with each antibody were scanned daily from day 1 to day 6. All other patients had scans performed from day 3 to day 6. The scans were reported 'blindly' by two nuclear medicine specialists, and the results were compared with the findings at operation or endoscopic laser therapy.

Measurement of antibody uptake by tumours and tissues

Surgery was performed at day 6 after radiolabelled antibody injection. Twelve patients administered with radiolabelled M8 and five patients with radiolabelled 77-1 had samples of cancer and normal tissues taken at the time of surgery (resected specimen, normal colon, wound edge muscle, subcutaneous fat and venous blood sampling) for direct measurement of radiolabel uptake.

All specimens were put into scintillation tubes and counted in a γ-scintillation counter (LKB Ultrogamma 2, Pharmacia LKB, Milton Keynes, UK). The radioactivity was expressed as c.p.m./g tissue. The relative uptake of radioactivity by the tumours and tissues was expressed as a ratio to that of blood (tissue c.p.m./g to blood c.p.m./g). The uptake of activity by the tumours was expressed as a ratio to that of the normal colon. The localization to the tumours and tissues for each antibody was compared using Student's paired t test. The localization results for M8 and 77-1 were compared by means of Student's unpaired t test (computer program StatWorks®, Cricket Software Incorporated, Philadelphia, USA). The numbers of tumours detected by each monoclonal antibody were compared by the χ^2 test.

Immunohistochemistry

Tumour tissue was obtained at the time of surgery or from endoscopic biopsies. Formal saline fixed histological sections, diagnosed as cancer by histopathologists at University College Hospital, were used for immunohistochemical study. An indirect immunoperoxidase method was used[10]. Sections were incubated with the undiluted hybridoma supernatants for 1 h. They were then washed with Tris (Sigma) buffered saline (pH 7·6) and incubated for 30 min with rabbit anti-mouse immunoglobulin conjugated to peroxidase (Dakopatts, High Wycombe, Bucks, UK). The reaction product was developed using diaminobenzidine tetrahydrochloride (Sigma). A colorectal cancer section with known positive reaction to the monoclonal antibodies was included in each staining study to ensure that all reagents were reactive. Negative control consisted of the same colorectal section but without the addition of first antibody. The staining results were expressed as either positive or negative. Any equivocal staining was scored as negative.

Results

No untoward side-effects or abnormalities in hepatic or renal function were found 2 weeks after antibody administration. For both radiolabelled M8 and 77-1, γ camera scans could be obtained between days 3 and 6 (*Figure 1*).

Radioimmunolocalization with M8

Positive scans were obtained from 13 cancers (six sigmoid/rectosigmoid, two caecal, one hepatic flexure and four rectal cancers, of which two were recurrent rectal cancers) in 16 patients. Hepatic metastases in five patients (three with primary and two with recurrent cancers) were not detected because of high uptake of radiolabel by the liver. Taking liver metastases into consideration, a total of 21 tumour sites were present and 13 were detected by M8.

All scan-positive tumours had positive immunohistochemistry with M8. Negative scans were obtained from two patients who had rectal cancers and one patient who had recurrent sigmoid cancer; two of these cancers stained negatively but one stained positively with M8. The sizes of tumour detected ranged from 2 × 2 to 7 × 7 cm. The mean(s.d.) tumour to normal colon ratio in 12 patients was 2·5(1·2). The mean(s.d.) tumour to blood ratio was 4·9(3·7), which was significantly higher than the mean tissue to blood ratios (*Figure 2*): normal colon, 2·0(1·6) ($P=0·002$); subcutaneous fat, 1·1(1·6) ($P=0·012$); and muscle, 0·8(0·4) ($P=0·004$).

Radioimmunolocalization with 77-1

Positive scans were obtained in ten (three sigmoid, of which one was a recurrent cancer, one caecal, and six rectal cancers, of which one was a recurrent rectal cancer) of the 15 cancers present in 14 patients. High hepatic uptake of the radiolabel

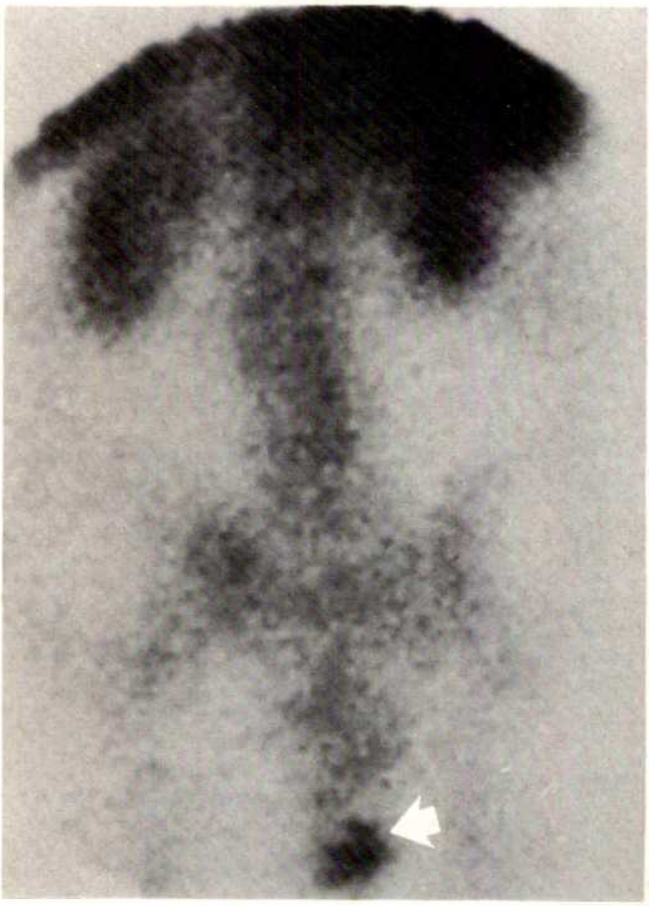

Figure 1 *Positive γ camera scan taken posteriorly showing the radioimmunolocalization of a rectal cancer (arrow) by* ^{111}*In-labelled 77-1. Note the uptake of radiolabel in the surrounding bones, kidneys and liver*

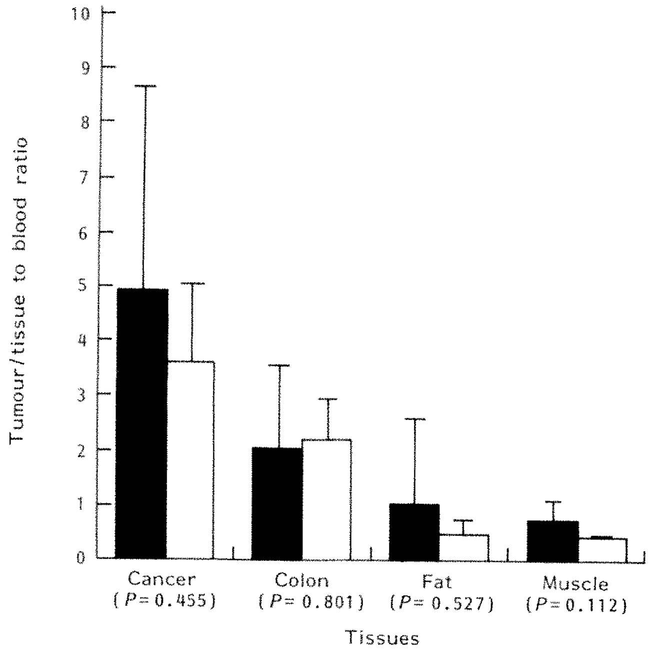

Figure 2 *The mean(s.d.) tumour to blood ratios of ^{111}In-labelled M8 (■) and ^{111}In-labelled 77-1 (□) were significantly higher than the corresponding tissue to blood ratios* ($P=0{\cdot}009$–$0{\cdot}041$). *There was no significant difference between the uptake of M8 and 77-1 by individual tissues (see* P *values). Bars represent standard deviations*

prevented the detection of three liver metastases. Including hepatic metastases, the radiolabelled 77-1 detected 10 of 18 tumour sites.

The specimens of cancer from nine patients who had positive scans stained positively with 77-1. Three patients who had negative scans had sigmoid cancers which stained positively with 77-1. No cancer specimens were available for staining in two patients: a patient with sigmoid cancer had a negative scan, and a patient with recurrent rectal cancer had a positive scan. A patient who had a negative scan also had a caecal cancer, which did not react with 77-1 on immmunohistochemistry. The tumours detected ranged in size from 3 × 2·5 cm to 10 × 10 cm. The mean(s.d.) tumour to normal colon ratio in five patients was 1·6(0·5). The mean(s.d.) tumour to blood ratio was 3·6(1·5), which was significantly higher than the mean tissue to blood ratios (*Figure 2*): normal colon, 2·2(0·8) ($P=0{\cdot}041$); subcutaneous fat, 0·5(0·3) ($P=0{\cdot}011$); and muscle, 0·5(0·0) ($P=0{\cdot}009$).

Comparison of M8 and 77-1 results

Although the tumour to normal colon ratios achieved by M8 were higher than those obtained with 77-1 (*Figure 3*), they were not statistically significant ($P=0{\cdot}141$). The tumour and tissue to blood ratios of M8 and 77-1 are compared in *Figure 2*, which shows that the uptakes of either antibody by the tumours and tissues were similar and there were no statistically significant differences ($P=0{\cdot}112$–$0{\cdot}801$). There was no statistical difference between the number of tumours detected by the radiolabelled M8 (13 of 16) and 77-1 (10 of 15), $\chi^2=0{\cdot}295$ and $P>0{\cdot}5$.

Discussion

The present study has confirmed the immunohistochemical staining reaction of M8 and 77-1 with colonic cancer tissues. It has demonstrated their use, labelled with ^{111}In, in the radioimmunolocalization of colorectal cancers which were confirmed at operation or at endoscopy and histologically. ^{111}In-labelled M8 detected 13 of 16 cancers and 77-1 detected 10 of 15 cancers.

There are several reports of radioimmunolocalization of colorectal cancer using ^{131}I-labelled monoclonal antibodies; for example, MAb 19-9 (Reference 3), MAb 17-1 (Reference 4), a combination of three MAbs (anti-CEA MAb 202, MAb 17-1A and 19-9)[20], MAb 791T/36 (Reference 7), and a goat anti-CEA or a mouse monoclonal anti-CEA antibody[21]. These antibodies gave a detection rate for colorectal cancer of between 54 and 94 per cent. An anti-CEA MAb labelled with ^{111}In detected all seven primary colorectal carcinomas, and eight of 11 metastastic tumours[22].

The optimal imaging time was found to be from day 3 onwards, as the background radioactivity was reduced with the clearance of the radiolabel from the circulation and excretion in the urine, while the radiolabel bound to the cancer remained high[22]. There was no significant difference between the mean tumour to normal colon ratios for ^{111}In-labelled M8 (2·5) and 77-1 (1·6), which are within the ranges reported for positive imagings[22]. The results are similar to other reports; for example, the ratios were 2·8 for MAb 791T/36 (Reference 23), 2·6–3·0 for MAbs 19-1 and 17-1 (Reference 3), 3·0 for MAb 17-1 (Reference 4), and 2·1 for MAb ICR2, a rat anti-EMA MAb (Reference 24). An anti-CEA MAb C46 achieved a ratio of 5·8 (Reference 22). The tissue to blood ratios were similar for both 77-1 and M8, indicating that the tissue localizations of the two radiolabelled antibodies were similar *in vivo*. In the context of antibody-targeted therapy, a greater tumour to normal colon ratio may be required.

None of the hepatic metastatic disease was detected by M8 or 77-1 because of high radiolabel uptake by the liver. The accumulation of radioactivity in the liver is probably caused by high uptake by the reticuloendothelial system of the ^{111}In released by the DTPA linker[25]. New and more stable conjugates are being prepared to overcome this problem[26]. Alternatively, ^{131}I-labelled antibodies can be used to detect liver metastases by means of a computer-assisted subtraction of background radioactivity, or the use of a second antibody to remove non-targeted first antibody to enable a high early tumour to non-tumour ratio to be achieved[27]. Recently, ^{99m}Tc-labelled monoclonal antibodies have been shown to be effective in detecting colorectal cancer and hepatic metastases[28]. Unlike ^{111}In-labelled antibodies, γ camera images may be acquired on the day of administration of ^{99m}Tc-labelled antibodies.

There was a correlation between the results of imaging and immunohistochemistry, as all patients having a positive scan had tumours which stained with M8 or 77-1. Three patients

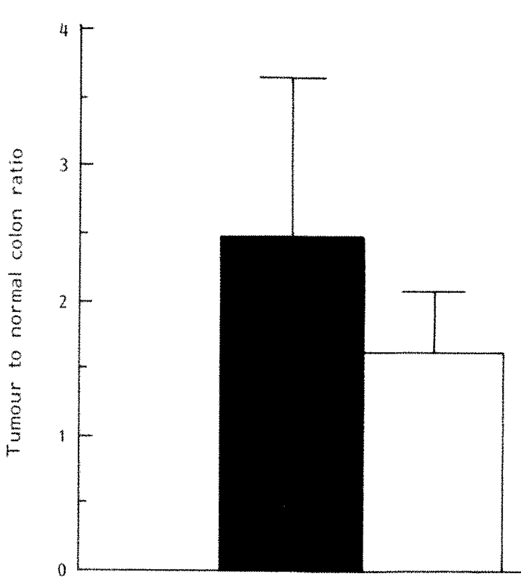

Figure 3 *There was no significant difference between the mean(s.d.) tumour to normal colon ratios of the ^{111}In-labelled M8 (■) and ^{111}In-labelled 77-1 (□)* ($P=0{\cdot}141$). *Bars represent standard deviations*

with negative scans also had negative staining with the antibodies. This correlation might enable the selection of appropriate monoclonal antibodies for immunolocalization. Antibody-targeted therapy, by means of prior immunohistochemical staining of endoscopic biopsies, may be feasible[29]. One cancer in the M8 and three in the 77-1 group reacted with the antibodies on staining, but the scans were negative. This finding has been reported by others[5]. The relative importance of the site, size or antigen expression of the tumours in relation to the results of the imaging has yet to be established[30]. The use of antibody Fab fragment may be better than the use of intact antibody for tumour localization[5]. A 'cocktail' of monoclonal antibodies, each recognizing a distinct antigenic epitope on a cancer, may improve successful immunolocalization[31].

M8 and 77-1 recognize epitopes of a cell surface glycoprotein called EMA[14,15]. This is present on the cell surface of most epithelial tumours[16] and colorectal cancers[10]. Antibodies with a high affinity to EMA may have potential for the immunoscintigraphy of a wide variety of epithelial tumours.

Acknowledgements

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References

1. Goldenberg DM, Deland F, Kim E *et al.* Use of radiolabelled antibodies to carcinoembryonic antigen for the detection and localisation of diverse cancers by external photoscanning. *N Engl J Med* 1978; **298**: 1384–8.
2. Kohler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. *Nature* 1975; **256**: 495–7.
3. Chatal JF, Saccavini JC, Fumoleau P *et al.* Immunoscintigraphy of colon carcinoma. *J Nucl Med* 1984; **25**: 307–14.
4. Mach JP, Chatal JF, Lumbrusco JD *et al.* Tumour localisation in patients by radiolabelled monoclonal antibodies against colon carcinoma. *Cancer Res* 1983; **43**: 5593–600.
5. Colcher D, Esteban J, Carrasqillo JA *et al.* Quantitative analyses of selective radiolabelled monoclonal antibody localisation in metastatic lesions of colorectal cancer patients. *Cancer Res* 1987; **47**: 1185–9.
6. Armitage NC, Perkins AC, Pimm MV. Imaging of bone tumours using a monoclonal antibody raised against human osteosarcoma. *Cancer* 1986; **58**: 37–42.
7. Armitage NC, Perkins AC, Pimm MV, Farrands PA, Baldwin RW, Hardcastle JD. The localisation of an anti-tumour monoclonal antibody (791T/36) in gastrointestinal tumours. *Br J Surg* 1984; **71**: 407–12.
8. Edwards PAW. Heterogenous expression of cell-surface antigens in normal epithelia and their tumours, revealed by monoclonal antibodies. *Br J Cancer* 1985; **51**: 149–60.
9. Jaffers GJ, Fuller TC, Cosimi AB, Russell PS, Winn HJ, Colvin RB. Monoclonal antibody therapy: anti-idiotypic antibodies to OKT3 arising despite intense immunosupression. *Transplantation* 1986; **41**: 572–8.
10. Yiu CY, Baker L, Gusterson BA *et al.* Monoclonal antibodies reacting with colorectal tumours. *Anticancer Res* 1986; **6**: 721–4.
11. Foster CS, Edwards PAW, Dinsdale EA, Neville AM. Monoclonal antibodies to the human mammary gland. I. Distribution of determinants in non-neoplastic mammary and extramammary tissues. *Virchows Arch* [*A*]1982; **394**: 279–94.
12. Summerhayes IC, McIlhinney RAJ, Ponder BAJ, Shearer RJ, Pocock RD. Monoclonal antibodies raised against cell membrane components of human bladder tumour tissue recognising subpopulations in normal urothelium. *J Natl Cancer Inst* 1985; **75**: 1025–32.
13. McIllhinney RAJ, Patek S, Gore M. Monoclonal antibodies recognizing epitopes carried on both glycolipids and glycoproteins of the human milk flat globule membrane. *Biochem J* 1985; **227**: 155–62.
14. Heyderman E, Steele K, Ormerod MG. A new antigen on the epithelial membrane: its immunoperoxidase localisation in normal and neoplastic tissues. *J Clin Path* 1979; **32**: 35–9.
15. Sloane JP, Ormerod MG. Distribution of epithelial membrane antigen in normal and neoplastic tissues and its value in diagnostic tumour pathology. *Cancer* 1981; **47**: 1786–95.
16. Pinkus GS, Kurtin P. Epithelial membrane antigen: a diagnostic discriminant in surgical pathology. *Hum Pathol* 1985; **16**: 929–40.
17. Rainsbury RM. The localisation of human breast carcinomas by radiolabelled monoclonal antibodies. *Br J Surg* 1984; **71**: 805–12.
18. Yiu CY, Baker L, Boulos PB. Immunolocalisation of an anti-EMA monoclonal antibody to a renal carcinoma xenograft. *Anticancer Res* 1990; **10**: 1775–8.
19. Hnatowich DJ, Layne WW, Childs RL. The preparation and labelling of DTPA coupled albumin. *Int J Appl Radiat Isotopes* 1982; **33**: 327–32.
20. Chatal JF, Douillard JY, Saccavini JC *et al.* Clinical prospective study with radioiodinated monoclonal antibodies directed against colorectal cancer. In: Baldwin RW, Byers VS, eds. *Monoclonal Antibodies for Cancer Detection and Therapy.* London: Academic Press, 1985: 159–80.
21. Begent RHJ, Keep PA, Searle F *et al.* Radioimmunolocalization and selection for surgery in recurrent colorectal cancer. *Br J Surg* 1986; **73**: 64–7.
22. Armitage NC, Perkins AC, Durrant LG *et al. In vitro* binding and *in vivo* localization in colorectal cancer of a high affinity monoclonal antibody to carcinoembryonic antigen. *Br J Surg* 1986; **73**: 965–9.
23. Armitage N. The localization of anti-tumour monoclonal antibodies in colorectal cancer. *Ann R Coll Surg Engl* 1986; **68**: 302–6.
24. Davidson BR. An evaluation of epithelial membrane antigen as a target for monoclonal antibodies in the investigation of patients with colorectal cancer. *MD Thesis,* University of Glasgow, 1989.
25. Goldenberg DM. Immunological approaches for early cancer detection. *Recent Results Cancer Res* 1988; **106**: 104–13.
26. Esteban JM, Schlom J, Gansow O. New method for the chelation of indium-111 to monoclonal antibodies: biodistribution and imaging of athymic mice bearing human colon carcinoma xenografts. *J Nucl Med* 1987; **28**: 861–70.
27. Sharkey RM, Primus FJ, Goldenberg DM. Second antibody clearance of radiolabelled antibody in cancer radioimmunodetection. *Proc Natl Acad Sci USA* 1984; **81**: 2843–6.
28. Granowska M, Mather SJ, Britton KE *et al.* ^{99m}Tc radioimmunoscintigraphy of colorectal cancer. *Br J Cancer* 1990; **62**(Suppl X): 30–3.
29. Lawson SM, Carrasquillo JA. Current status of radioimmunoimaging and therapy. In: Herberman RB, Wiltrout RH, Gorelik E, eds. *Immune Response to Metastases.* Vol II. Boca Raton, Florida: CRC Press, 1987: 117–26.
30. Blumenthal RD, Sharkey RM, Kashi R *et al.* Influence of animal host and tumor implantation site on radio-antibody uptake in the GW-39 human colonic cancer xenograft. *Int J Cancer* 1989; **44**: 1041–7.
31. Munz DL, Alavi A, Koprowski H, Herlyn D. Improved radioimaging of human tumor xenografts by a mixture of monoclonal antibody F(ab')2 fragments. *J Nucl Med* 1986; **27**: 1739–45.

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Malignancy following ureterosigmoidostomy in patients with exstrophy

Forty-two patients with exstrophy underwent a urothelial colonic anastomosis. Eight developed a tumour at the ureterocolic anastomosis and in another two patients a malignant lesion occurred in the bladder remnant.

Previous studies have shown a markedly increased (at least 100-fold) risk of malignancy associated with ureterosigmoidostomy[1-4]. Accurate assessment of the risk has not been possible because of inadequate data. This study used a long follow-up period in well defined groups of patients.

Patients and methods

One hundred and three patients, 29 girls and 74 boys, born with exstrophy before 1964 were treated at the Hospital for Sick Children and the St. Peter's Group of Hospitals (*Table 1*). Thirty-four patients had been initially diverted with a ureterosigmoidostomy, of whom 13 had subsequently had conversion to an ileal or colon conduit. The ureteric stumps had been left *in situ* within the colon.

Six patients had had a Gersuny operation (*Figure 1*), and two had later been converted to a colon conduit. The faecal and urinary streams should be separate, but retraction of the common wall between rectum and colon would allow mixing of the urine and faeces in a common reservoir. This could be seen at sigmoidoscopy. Two patients had had a vesicocolic anastomosis fashioned.

A total of 42 patients were in an 'at-risk' group of developing a tumour because there was, or had been, mixing of urinary and faecal streams at the urothelial–colonic anastomosis.

Sixty-one patients were in a 'low-risk' group, i.e. no mixing of the urinary and faecal streams. Fifteen patients had had a primary bladder closure, 36 had an ileal conduit, five had a cutaneous ureterostomy and five had a colon conduit.

Patients in the at-risk group had had an annual colonoscopy since the risk of tumour formation was recognized in 1980. Patients in the low-risk group were followed annually but colonoscopy was performed only if indicated by symptoms.

Results

Deaths

Eleven patients died, five in the low-risk group and six in the at-risk group (*Table 2*). In the at-risk group two patients died with a carcinoma in the bladder remnant at the ages of 34 and 28 years and two died with a carcinoma of the colon when aged 46 and 30 years (*Table 3*).

The first patient with carcinoma of the bladder was a male who had had his bladder exstrophy closed when aged 2 years. Two years later he had undergone a mucosal cystectomy and ureterosigmoidostomy which was later converted to an ileal conduit. He died aged 28 years from a carcinoma of the bladder remnant (according to his general practitioner's records) but there was no post-mortem examination. The second boy had had two attempted bladder closures and later underwent cystectomy and ureterosigmoidostomy. The ureterosigmoidostomy was converted to an ileal conduit when he was 20 years old. He presented at the age of 34 years with metastastic adenocarcinoma in the biceps muscle. He died 3 days after a laparotomy which revealed a necrotic mass in the pelvis. Post-mortem examination showed the tumour arising from the bladder remnant rather than the ureterosigmoidostomy.

Two patients died with a tumour at the ureterosigmoidostomy site 28 and 46 years after urinary diversion. The first patient had a ureterosigmoidostomy converted to an ileal loop at 12 years of age. At the age of 29 years she developed a poorly differentiated Dukes' C adenocarcinoma at the ureterocolic anastomosis and died a year later. The second patient was diverted with a ureterosigmoidostomy. At 40 years of age he developed an adenocarcinoma of the colon at the ureterocolic anastomosis, and died 6 years later.

Follow-up

Sixteen patients, 12 in the low-risk group, have been lost to follow-up. The at-risk group of 32 patients, mean age 36·1 years, continues follow-up. Two men had had a ureterosigmoidostomy performed as children and developed an adenocarcinoma at the ureterocolic anastomosis 28 and 33 years later (*Figure 2*). Both patients had a sigmoid colectomy and reimplantation of the ureters into the colon.

Four other patients in this group have developed non-invasive tumours at the ureterocolic anastomosis. All patients with non-invasive tumours had had their ureterosigmoidostomies converted to an ileal conduit years previously. They developed non-invasive tumours (benign polyps, adenoma and reactive polyp) 20, 31, 28 and 38 years after ureterosigmoidostomy.

Of the 49 patients in the low-risk group, none has developed benign or malignant colonic or bladder remnant tumours.

Discussion

There has recently been renewed interest in ureterosigmoidostomy as a urinary diversion[5], because of greater ability to prevent and treat metabolic and infective complications.

Leadbetter *et al.*[6] calculated the lifetime risk of developing a malignant tumour at the ureterosigmoidostomy as approximately 5 per cent. A more recent study showed an 11 per cent risk in those with a ureterosigmoidostomy of more than 15 years' duration[7]. In this study the risk of developing a malignant tumour at the ureterocolic anastomosis by 36 years of age was 11 per cent, with a further 11 per cent risk of developing non-invasive tumours.

In a survey by colonoscopy of 17 patients with a

Table 1 *Follow-up of 103 patients with exstrophy*

Original operation	No. of patients
At-risk patients (sometime mixed faecal/urine streams)	
Ureterosigmoidostomy	34 (13 with further diversion)
Gersuny operation	6
Vesicocolic anastomosis	2
Total	42
Low-risk patients (no mixing of streams)	
Ileal conduit	36
Primary bladder closure	15
Cutaneous ureterostomy	5
Colon conduit	5
Total	61

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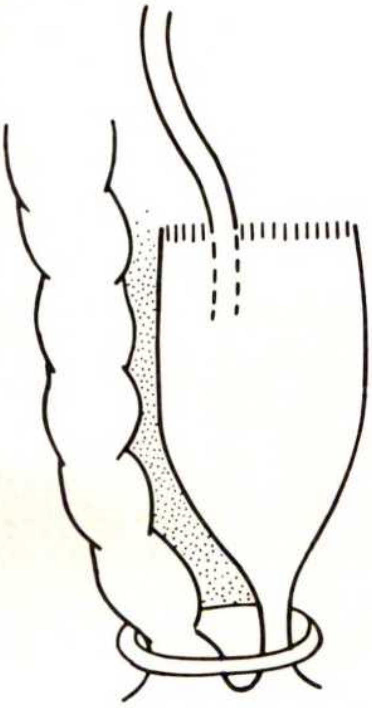

Figure 1 *Gersuny operation showing ureters entering rectum. The sigmoid colon is brought through the anal sphincter*

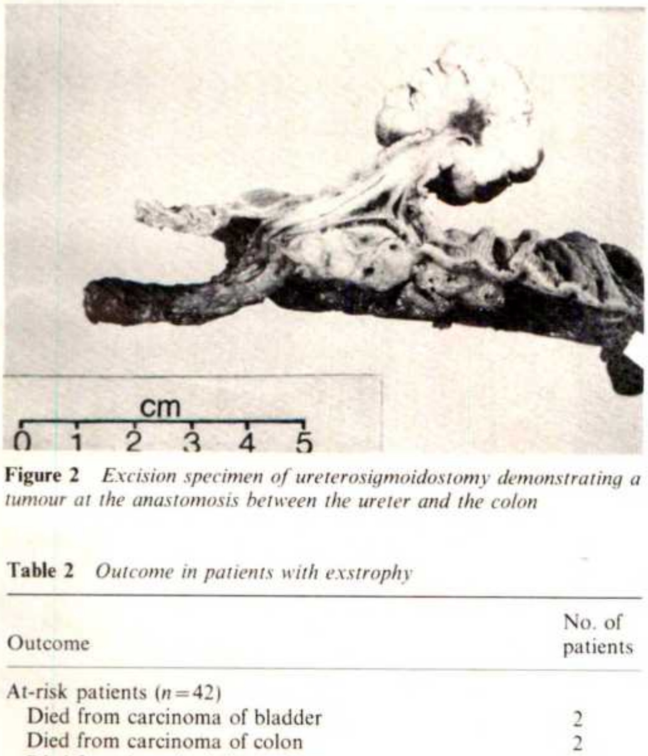

Figure 2 *Excision specimen of ureterosigmoidostomy demonstrating a tumour at the anastomosis between the ureter and the colon*

Table 2 *Outcome in patients with exstrophy*

Outcome	No. of patients
At-risk patients ($n = 42$)	
Died from carcinoma of bladder	2
Died from carcinoma of colon	2
Died from intestinal obstruction	1
Died from inhalation of vomit	1
Sigmoid colectomy, carcinoma of colon	2
Sigmoid colectomy, non-invasive tumour	4
Lost to follow-up	4
Continue follow-up	32*
Low-risk patients ($n = 61$)	
Died from renal failure	2
Died from intestinal obstruction	1
Died from poliomyelitis	1
Died, cause unknown	1
Lost to follow-up	12
Continue follow-up	44

*Includes 6 surviving patients who underwent sigmoid colectomy

Table 3 *Tumours in the at-risk group*

Age at ureterosigmoidostomy (years)	Age at tumour presentation (years)	Tumour site
4	28	Bladder tumour
4	34	Adenocarcinoma of bladder
1·5	29	Adenocarcinoma of colon
?	40	Adenocarcinoma of colon
3	31	Adenocarcinoma of colon
2	35	Adenocarcinoma of colon
6	44	Non-invasive tumour
5	36	Non-invasive tumour
2	22	Non-invasive tumour
7	35	Non-invasive tumour

ureterosigmoidostomy, seven were found to have polyps at a median of 30 years after diversion[8], while another study, with only 15 years of follow-up, described only one non-invasive tumour[5].

Williams *et al.*[9], in a prospective study, carried out post-mortem examination of the colon in 19 patients aged under 35 years for evidence of non-invasive tumours, and found none. Non-invasive tumours may develop into an adenocarcinoma of the colon[10]. Four patients with untreated non-invasive lesions took 5–10 years to develop malignant lesions[10].

The only large study of ureterosigmoidostomy and malignant risk was based on an assumed number of patients, with varied indications for diversion and inadequate follow-up[1]. Other studies had short follow-up, heterogeneous groups of patients, or small numbers[3–5].

The mean age of patients in the at-risk group in this study was 36·1 years. The cumulative risk of developing a rectosigmoid adenocarcinoma at this age in the normal population is 6·1 per 100 000[11]. Four of the 38 patients at risk who reached adulthood developed adenocarcinoma of the colon, giving an increased risk for this group of 1726 times the expected incidence.

Tumours of the exposed exstrophied bladder are predominantly adenocarcinomas, which O'Kane and Megaw[12] felt to be secondary to metaplasia of the urothelium. Culp[13] suggested the aetiology was linked to enteric nests within the urothelium. Glandular epithelium can be normal in the middle portion of the exstrophy bladder[14]. The tumour described here has not been reported before. The capacity of the closed bladder to develop a malignancy (especially after near-total cystectomy) must be limited. Although post-mortem evidence from one of the patients clearly indicated a bladder origin, the suspicion must remain that both bladder cancers were of ureterosigmoidostomy origin. No 'bladder cancers' have occurred in the low-risk group.

Annual colonoscopy should be carried out in patients with a ureterosigmoidostomy. Patients with residual ureteric stumps in 'dry' colons should undergo excision to obviate the need for colonoscopy. Tumours may occur in the exstrophied bladder remnant despite attempted cystectomy.

Acknowledgements

Figure 2 is presented courtesy of C. R. J. Woodhouse, from *Long-term Paediatric Urology*, Blackwell Scientific Publications Ltd., 1991.

References

1. Stewart M, Macrae FA, Williams CB. Neoplasia and ureterosigmoidostomy: a colonoscopy survey. *Br J Surg* 1982; **69**: 414–16.
2. Eraklis AJ, Folkman MJ. Adenocarcinoma at the site of ureterosigmoidostomies for exstrophy of the bladder. *J Pediatr Surg* 1978; **13**: 730–4.
3. Urdaneta LF, Duffell D, Creevy CD, Aust JB. Late development of a primary carcinoma of the colon following ureterosigmoid-

ostomy: report of three cases and literature review. *Ann Surg* 1966; **164**: 503–13.

4. Parsons CD, Thomas MH, Garrett RA. Colonic adenocarcinoma: a delayed complication of ureterosigmoidostomy. *J Urol* 1977; **118**: 31–4.
5. Stockle M, Becht E, Voges G, Riedmiller H, Hohenfellner R. Ureterosigmoidostomy: an outdated approach to bladder exstrophy? *J Urol* 1990; **143**: 770–5.
6. Leadbetter GW Jr, Zickerman P, Pierce E. Ureterosigmoidostomy and carcinoma of the colon. *J Urol* 1979; **121**: 732–5.
7. Zabbo H, Kay R. Ureterosigmoidostomy and bladder exstrophy: a long term follow up. *J Urol* 1986; **136**: 396–8.
8. Starling JR, Uehling DT, Gilchrist KW. Value of colonoscopy after ureterosigmoidostomy. *Surgery* 1984; **96**: 784–9.
9. Williams AR, Balasooriya BA, Day DW. Polyps and cancer of the large bowel: a necropsy study in Liverpool. *Gut* 1982; **23**: 835–42.
10. Muto T, Bussey HJ, Morson BC. The evolution of cancer of the colon and rectum. *Cancer* 1975; **36**: 2251–70.
11. Office of Population Censuses and Surveys. *Cancer Statistics Registrations* 1984; **16**: 32–3.
12. O'Kane HO, Megaw JMc. Carcinoma in the exstrophied bladder. *Br J Surg* 1968; **55**: 631–5.
13. Culp DA. The histology of the exstrophied bladder. *J Urol* 1964; **91**: 538–48.
14. Formiggini B. Contributo allo studio della mucosa vesicale extrofica. *Riforma Med* 1920; **36**: 252–4.

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Announcement

Royal College of Physicians and Surgeons of Glasgow FRCS Examinations

Examinations for the Surgical Fellowship will take place on the following dates:

Part A (Basic Sciences)

MCQ papers	Orals start	Closing date
13 January 1992	15 January 1992	2 December 1991
18 May 1992	20 May 1992	6 April 1992

Before admission to Part A, candidates must have held a medical qualification for not less than 2 years *recognized by the General Medical Council or acceptable to the Council of the College.*

Part B (Surgery in General)

Written paper	Orals start	Clinicals start	Closing date
24 October 1991	28 October 1991	11 November 1991	12 September 1991
23 January 1992	27 January 1992	10 February 1992	12 December 1991
28 May 1992	1 June 1992	15 June 1992	16 April 1992

Before admission to Part B, candidates must have been qualified for not less than 4 years, and have completed 2 years in clinical surgery posts recognized by the Council of the College, in addition to the pre-registration year. *They must have passed the Primary/Part A Examination of any of the UK and Irish Colleges or an equally recognized qualification listed in the regulations.*

Further information can be obtained from:

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Br. J. Surg. 1991, Vol. 78, October, 1219–1221

Schistosomiasis of the appendix

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The clinicopathological features of schistosomiasis of the appendix are discussed, based on the clinical presentation, operative findings and morphological changes in the specimens of patients seen in Ibadan between 1980 and 1989. Schistosoma haematobium *was implicated as the causal agent of a granulomatous inflammatory reaction with eosinophilia and fibrosis. Intramuscular oviposition was associated with frank acute appendicitis, and serosal involvement resulted in peritoneal adhesions, with ileoileal intussusception in one patient. The actual role of schistosomal infestation as a contributory factor in appendicitis is still open to debate, but the diagnosis must be entertained in patients in the tropics with features of acute appendicitis or recurrent abdominal pain.*

Schistosomiasis of the appendix was first described by Turner in 1909[1]. Most cases are attributed to *Schistosoma haematobium* among African patients[1–3], although mixed infections involving *S. haematobium* and *S. mansoni* have been reported[4]. In Hong Kong, appendicular schistosomiasis has been attributed to *S. japonicum*[5].

The actual role of schistosomal infestation in the aetiology of acute appendicitis has been the subject of some controversy[2,3], because in rural Egypt and parts of West Africa (where schistosomiasis is endemic) appendicitis is both relatively uncommon and not usually associated with schistosomal infestation of the appendix.

In this communication we report the clinicopathological findings in 15 cases of appendicular schistosomiasis seen at University College Hospital, Ibadan, Nigeria, over the 10-year period from 1980 to 1989.

Patients and methods

Fifteen cases of schistosomal appendicitis were identified from the 627 appendicectomy specimens received in the Department of Pathology during the study period. Eleven of these cases involved inpatients, and the clinical case notes of nine of them were retrieved from the Records Department to ascertain their clinical presentation, operative management and postoperative course. In four other patients, surgical management had been in peripheral hospitals, and their specimens were referred to the Pathology Department for histological examination. The gross and histological appearances of 13 cases were reviewed in detail.

Results

The clinical presentation, management and postoperative course of nine patients with appendicular schistosomiasis are shown in *Table 1*. All patients were males, their ages ranging from 10 to 44 years with a peak incidence in the third decade. Three of four patients who had full blood counts had significant eosinophilia of 8, 12 and 15 per cent respectively.

In four cases, the clinical presentation was with acute appendicitis. A single patient presented with recurrent right iliac fossa pain, and two others had appendiceal masses; these three patients underwent elective interval appendicectomy. The remaining two patients underwent incidental appendicectomy, in one during the course of vagotomy and pyloroplasty for chronic duodenal ulcer, and in the other during operation for acute intestinal obstruction secondary to ileoileal intussusception. In this latter patient, no leading point was found but there were serosal seedlings. None of the nine patients presented clinically with haematuria. Three subsequently developed postoperative wound infection.

In the 13 patients whose histological and gross appearances were reviewed, diagnosis was based on the demonstration of calcified or uncalcified schistosome ova (*Figure 1*) which were most frequently situated in the submucosal or serosal layers, usually being most numerous in the submucosa (*Table 2*).

In five of these cases there was transmural oviposition, while in three others the ova were restricted to the serosa of the appendix. The ova were identified as those of *S. haematobium* in nine cases, but in the remaining four were too distorted for taxonomic classification. Neither schistosomes nor adult worms were identified in any of the cases examined.

Nine patients were treated surgically at University College Hospital. In four of five patients with transmural oviposition, the appendix was acutely inflamed both macroscopically and on histological examination. In three patients who had evident fibrous peritoneal adhesions there were serosal granulomas. The appendix was macroscopically normal in two patients, one of whom had only submucosal oviposition, and the second of whom had both submucosal and intramuscular oviposition.

The most characteristic tissue response to the schistosome ova was the formation of surrounding epithelioid and giant cell granulomas around viable uncalcified or dead calcified ova in the wall of the appendix. In three cases there was complete fibrous replacement and hyalinization of the granulomas, while in two others pink homogeneous granular deposits were observed around the schistosome ova – the Splendore–Hoeppli phenomenon (*Figure 2*).

Prominent tissue eosinophilia was present in six cases and was marked in two appendices, with the formation of eosinophilic microabscesses in one instance. Eosinophilia was most prominent in the absence of significant fibrosis of the appendix.

Submucosal fibrosis of the appendix occurred in ten cases, and acute suppurative inflammation occurred in five (*Table 2*).

Lymphoid follicle atrophy was found in four patients and resulted from extensive submucosal fibrosis; in four other patients there was hyperplasia of the lymphoid follicles. Prominent reactive lymphoid follicles with germinal centres were present in three of the cases. Other non-specific histological findings included endarteritis obliterans and foci of old and present haemorrhage.

Discussion

The incidence of acute appendicitis in African patients has been increasing in recent years[1,6]. Possible reasons for this trend include Westernization of the indigenous African's diet[6], improved housing and water supply[7], heightened community awareness[8] and, more recently, infection by *Yersinia enterocolitica* predisposing the appendix to secondary bacterial infection[9,10].

Despite the relatively high prevalence of acute appendicitis in our environment[6], it is not commonly associated with schistosomiasis[1,2]. Thus in the present series only 2·4 per cent

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Table 1 *Clinical features of nine patients with appendicular schistosomiasis*

Patient no.	Sex	Age (years)	Presentation	Operation	Complication
1	M	10	Acute appendicitis	Appendicectomy	—
2	M	20	Acute appendicitis	Appendicectomy	Wound infection
3	M	21	Ruptured appendix	Appendicectomy	Wound infection
4	M	23	Acute appendicitis	Appendicectomy	—
5	M	25	Appendiceal mass	Interval appendicectomy	—
6	M	26	Chronic duodenal ulcer	Incidental appendicectomy	—
7	M	28	Appendiceal mass	Interval appendicectomy	—
8	M	30	Recurrent right iliac fossa pain	Interval appendicectomy	—
9	M	44	Intussusception	Incidental appendicectomy	Wound infection

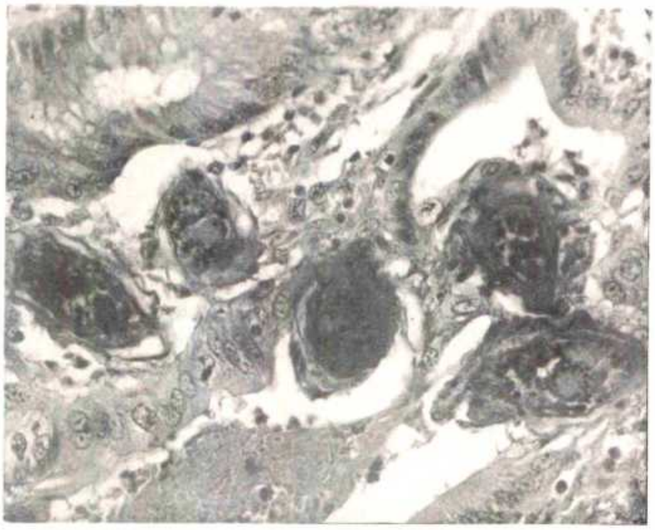

Figure 1 *Schistosome ova surrounded by intestinal glands (haematoxylin and eosin stain, × 290)*

Table 2 *Pathological features of 13 cases of schistosomiasis of the appendix*

Features	No. of cases
Ova	
Submucosal	10
Serosal	9
Muscularis propria	5
Mucosal	4
Tissue response	
Submucosal fibrosis	10
Granulomatous inflammation	9
Tissue eosinophilia	6
Acute suppurative inflammation	5
Splendore–Hoeppli reaction	2
Submucosal lymphoid follicles	
Atrophy	4
Hyperplasia	4

of all the appendicectomy specimens received during the 10-year period of the study contained schistosome ova. This is similar to the reported incidence of 2·9 per cent among Ghanaian patients[1]. By contrast, Chan *et al.*[5] recorded only 22 (0·2 per cent) of 12 538 appendices in their patients in Hong Kong as showing schistosomiasis. Because schistosomiasis is an endemic disease in this environment[11], the infrequency of association between schistosomiasis and appendicitis argues against a causal relationship.

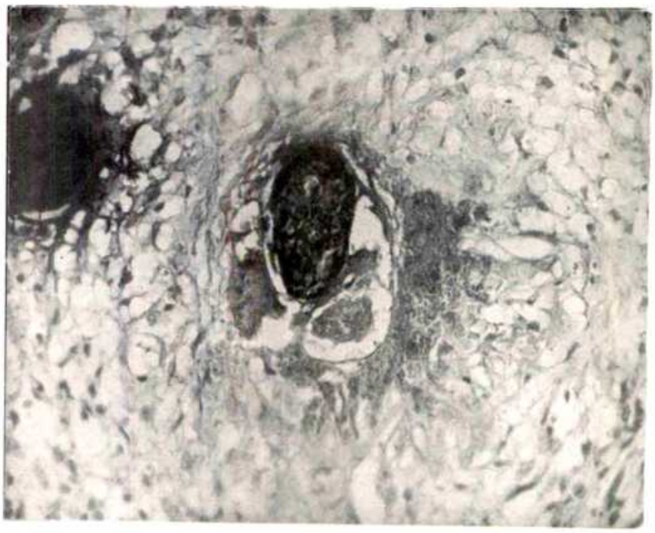

Figure 2 *Granuloma containing schistosome ovum surrounded by eosinophilic hyaline deposit (Splendore–Hoeppli reaction) (haematoxylin and eosin stain, × 290)*

The peak age for incidence in our patients with schistosomiasis was in the third decade, with a mean age of 23 years, which is higher than the mean age of 14 years in Hodasi's series[1]. However, the peak age for incidence in our patients coincides with that of patients with acute appendicitis generally in this environment[6], although this may be a fortuitous association.

The predominant mode of presentation of the present patients was with an acute abdomen. The diagnosis of schistosomal appendicitis is invariably retrospective since the clinical presentation and operative findings closely simulate those of acute pyogenic appendicitis[1]. As previously observed by Onuigbo[12], frank appendicitis in the present series was associated with intramuscular oviposition. In addition, serosal oviposition resulted in subsequent fibrous adhesions. Two patients had an appendiceal mass, which is another recognized mode of presentation in this environment[12].

Although *S. haematobium* is the commonest cause of the appendicular lesion in Africans[1–3], patients generally do not present with haematuria[2], which further militates against preoperative diagnosis of schistosomiasis.

The characteristic pathological tissue response to schistosome ova in the appendix is with granulomatous inflammation, and the lesions are most often situated in the submucosa and serosa. In the initial stages, well formed epithelioid cell granulomas are found, and these eventually undergo fibrous replacement with hyalinization[1]. The Splendore–Hoeppli reaction observed in two cases is believed to represent deposition of immune complexes around schistosome ova and was noted by Hoeppli in 1932[11]. Granulomatous lesions in the appendix in this environment may less often result from tuberculosis, foreign body reaction, fungal infections, sarcoidosis or, rarely, Crohn's disease[5,13]. By contrast, Crohn's disease is the usual cause of granulomatous disease in the vermiform appendix in Caucasians[13].

Tissue eosinophilia was seen in six cases and was most prominent in the earlier stages in the absence of significant fibrosis. This is similar to the observation of Lovett-Campbell and Rose[3] that the earliest lesions of schistosomiasis of the appendix are granulomas and eosinophilic inflammatory cellular infiltrates.

In summary, the confirmation of appendicular schistosomiasis is purely histological, because there are no pathognomonic clinical or operative findings[1]. However, schistosomiasis is a distinct entity which must be considered in patients in the tropics with acute appendicitis or chronic recurrent abdominal pain[1].

References

1. Hodasi M. Schistosoma appendicitis. *Trop Doct* 1988; **18**: 105–6.
2. Hughes M. A case of bilharzia of the appendix with strangulation of the ileum. *Br J Surg* 1949; **36**: 428–9.
3. Lovett-Campbell AE, Rose AN. Bilharsial appendicitis in *Schistosoma haematobium* infestation – a preliminary report. *Trans R Soc Trop Med Hyg* 1936; **30**: 335–44.
4. Iozzi S, Piva P, Savioli C. Acute intestinal infection from a granuloma due to *Schistosoma haematobium* in the appendix. *Trop Geogr Med* 1984; **36**: 87–9.
5. Chan KW, Eu KH, Ling J. The pathology of the appendix in Hong Kong. *Br J Clin Pract* 1988; **42**: 241–4.
6. Adekunle OO, Funmilayo JA. Acute appendicitis in Nigeria. *J R Coll Surg Edinb* 1986; **31**: 102–5.
7. Barker DJP, Morris J. Acute appendicitis, bathrooms and diet in Britain and Ireland. *Br Med J* 1988; **296**: 953–5.
8. Onuigbo WIB. An index of community awareness of appendicitis. *Trop Doct* 1983; **13**: 134–5.
9. Atwood SEA, Cafferkey MT, Keane FBV. *Yersinia* infection in surgical practice. *Br J Surg* 1989; **76**: 499–504.
10. Taylor J. Reviews in medicine: general surgery. *Postgrad Med J* 1990; **66**: 339–55.
11. Edington CM, Gilles HM. *Pathology in the Tropics*. London: Edward Arnold, 1979: 154 pp.
12. Onuigbo WIB. Resolution of the appendiceal mass in Nigerian Igbon. *Dis Colon Rectum* 1977; **20**: 679–80.
13. Allen DG, Biggart JD. Granulomatous disease in the vermiform appendix. *J Clin Pathol* 1983; **36**: 632–8.

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Case report

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Subtotal hepatectomy: a new procedure based on the inferior right hepatic vein

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Normally there are three major hepatic veins and a variable number of inferior accessory veins. The not infrequent existence of a few larger branches has been appreciated since the work of Couinaud[1] and others[2]. Recent developments in imaging modalities, particularly intraoperative ultrasonography, have allowed details in individual patients to assume clinical importance. This practical assessment of the intrahepatic vascular and biliary arrangement has allowed resectional surgery to advance to the stage of anatomically-based segmental resections (or preservations). A new hepatic resection based on the recognition and utilization of the inferior right hepatic vein is described.

Case report

The patient was a 48-year-old woman who presented with a 6-month history of epigastric fullness. For 1 month she had experienced epigastric pain and intermittent fever. She was otherwise well and specifically showed no weight loss nor other symptoms which could be referred to the gastrointestinal tract.

Physical examination confirmed an epigastric mass, and a provisional diagnosis of hepatic tumour was made. Her α-fetoprotein level was 480 ng/dl (normal range 1–10 ng/dl). Computed tomography (CT) scanning showed a 10 × 12 cm tumour in the left lobe of the liver (*Figure 1*), with extension to the right. A large inferior right hepatic vein was noted to be draining an uninvolved portion of the right liver. Coeliac angiography confirmed the findings and demonstrated marked compression of the retrohepatic vena cava.

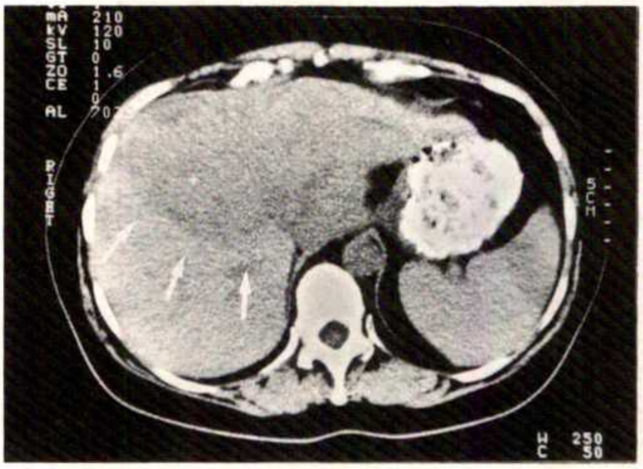

Figure 1 *Computed tomography scan showing extent of hepatic involvement by primary hepatocellular carcinoma extending to segment V/VIII (arrows). Excellent perfusion and size of segment VI and VII suggests there must be adequate venous drainage*

At laparotomy a huge tumour was found with several satellite lesions. As well as the left liver, it was apparent that segments IV, V and VII were involved. The clinical impression was of unresectability. Intraoperative ultrasonography, however, revealed a large inferior right hepatic vein draining segment VI and the inferior part of segment VII. It became apparent that it was, in theory, possible to resect the tumour, preserving enough viable liver based on the inferior right hepatic vein to be compatible with survival. Frozen section of the hepatoduodenal ligament showed no evidence of metastases and a modified extended left hepatic resection was therefore carried out. Resection of the tumour was as for an extended left hepatectomy[3], but after identification and preservation of the inferior right hepatic vein and mobilization of the left liver as far as possible all three major hepatic veins were ligated. Dissection from the hilum was then performed into the right liver (using

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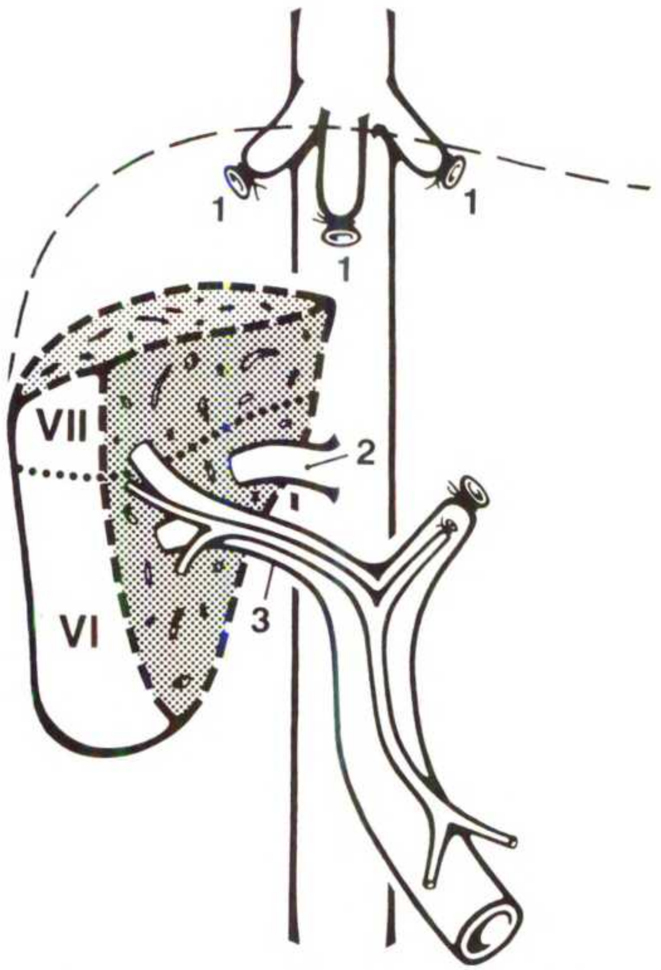

Figure 2 *Diagram of remnant after resection, showing ligated hepatic veins (1), inferior right hepatic vein (2) and right portal vein (3)*

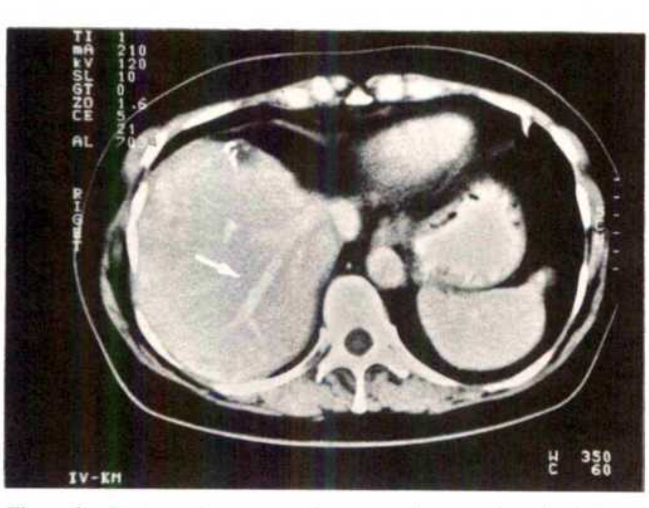

Figure 3 *Postoperative computed tomography scan through the lower part of the liver showing the right inferior hepatic vein (arrow)*

the jet dissector[4]) in a tangential fashion, preserving only segment VI and the dorsocranial part of segment VII (*Figure 2*). The remnant based on the inferior right hepatic vein was clinically viable.

Blood loss was 600 ml and the patient made an uneventful recovery. Histology showed hepatocellular carcinoma. She remains alive and well after 6 months, but has developed recurrent disease. A CT scan taken 4 months after operation showed hypertrophy of the remnant, absence of all three hepatic veins, but preservation of the inferior right hepatic vein (*Figure 3*).

Discussion

Preservation of as much viable liver substance as possible during major liver resections remains a priority. In this patient it was possible to preserve sufficient liver tissue because of the recognition and subsequent identification of an inferior right hepatic vein of adequate size draining an apparently unaffected part of the hepatic parenchyma.

Veins such as the one utilized in this patient have been described in as many as 10–24 per cent of patients[5]. Hypertrophy of the vein is likely if it is draining an area of liver that has had to increase its functional contribution.

The clinical importance of this vein has been discussed and utilized by Makuuchi *et al.*[5], who were able to preserve the inferior portion of the right liver in four patients. The technique was used to preserve liver tissue that would normally have been resected, thereby augmenting the function of the left-sided remnant. The logical conclusion was that it would have been technically feasible to preserve liver based on this vein alone, but it had never been demonstrated that residual function would allow survival, even with hypertrophy of the remnant. This case demonstrates the possibility of such a 'subtotal hepatic resection', and, since this vein is known to be the largest of the 'accessory' veins[6], awareness of this possibility and preoperative recognition may occasionally render very large or inaccessible tumours resectable.

Acknowledgements

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References

1. Couinaud C. Etudes anatomiques et chirurgicales. In: Couinaud, C, ed. *Le Foie*. Paris: Masson et Cie, 1957; 187–208.
2. Prieschnig A. Segmentresektionen. In: Prieschnig A, ed. *Leberresektionen*. Munich: Urban and Schwarzenberg, 1986: 198–200.
3. Blumgart LH. Liver resection – liver and biliary tumours. In: Blumgart LH, ed. *Surgery of the Liver and Biliary Tract*. Vol. 2. Edinburgh: Churchill Livingstone, 1988: 1268–70.
4. Baer HU, Maddern GJ, Blumgart LH. A new water-jet dissector – initial experience in hepatic surgery. *Br J Surg* 1991; **78**: 502–3.
5. Makuuchi M, Hasegawa H, Yamazuki S, Bandai Y, Watanabe G, Ito T. The inferior right hepatic vein: ultrasonic demonstration. *Radiology* 1983; **148**: 213–17.
6. Couinaud C. Heptatectomies through the main portal fissure. In: Couinaud C, ed. *Controlled Hepatectomies and Exposure of the Intrahepatic Bile Ducts. Anatomical and Technical Study*. Paris: Couinaud, 1981: 65–71.

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Management of haemangioma of the liver: comparison of results between surgery and observation

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Cavernous haemangioma of the liver was diagnosed in 33 patients using hepatic angiography between 1978 and 1988. Thirteen of these patients underwent surgery. There were no deaths after operation; morbidity included upper gastrointestinal bleeding in two patients and liver dysfunction in one. The follow-up study showed no evidence of recurrence in any of the 13 patients up to 143 months after operation. In the operated patients, a small haemangioma was left in the liver of two for anatomical reasons, but the size of these tumours showed no change over 3 years. The remaining 20 patients had no specific treatment for haemangioma and were followed up for between 18 months and 8 years. Of these 20 patients, 19 had tumours of <5 cm in size. As there was no enlargement or rupture of haemangiomas of <5 cm, it was felt that these could be observed. Cases having a potential for exposure to trauma, rapid tumour growth, or displaying severe symptoms should be considered for surgical treatment; this can be justified due to low morbidity and no mortality.

Cavernous haemangioma is the most common benign tumour of the liver[1,2]. An autopsy series has reported that the incidence of this tumour is about 2 per cent[3]. Ruptures of haemangioma are only rarely seen[4–6]. However, the incidence of rupture and the natural history of this lesion have yet to be clearly defined. The indications for operating on these lesions also remain unclear. To address these points, the clinical data of patients with hepatic haemangioma treated at our clinic were reviewed.

Patients and methods

From 1978 to 1988, 33 cases were diagnosed by hepatic angiography as haemangioma of the liver. When a hepatic tumour was found on non-invasive imaging studies, hepatic angiography was performed both to diagnose accurately small lesions under suspicion of being hepatocellular carcinoma and to investigate the vascular structure of the liver in larger lesions which might require surgical treatment. The patients comprised 17 men and 16 women, ranging in age from 37 to 70 years, with a mean of 51 years. No patient was pregnant and all denied ever having used oral contraceptives. Six patients had symptoms consisting of either epigastric pain (three patients) or back pain (three patients). The remaining 27 patients were not considered to have any symptom due to haemangioma. None had Kasabach-Merritt syndrome, a giant haemangioma and bleeding tendency induced by the consumption of platelets and coagulation factors due to local hypercoagulation in the capillary vessels of the tumour.

Ten patients (30 per cent) had multiple tumours and 23 (70 per cent) had a solitary tumour. The lesions in 22 (67 per cent) were located in the right lobe, and in ten (30 per cent) in the left lobe. Only one patient had bilateral haemangiomas. With regard to tumour size, ten were <2 cm in diameter, ten ranged from 2 to 5 cm, nine ranged from 5 to 10 cm and four were >10 cm. No correlation between tumour size and age was observed. Men tended to have smaller tumours than women, but this difference was not significant. Haemangiomas in 12 of 13 cases >5 cm in size were located on the surface of the liver.

There were 13 patients who had surgery and 20 who did not. Indications for operation were derived from previously published criteria[1,4,7,8] as follows: (1) tumours >5 cm in diameter, particularly if there is a potential for exposure to trauma; (2) symptoms, such as pain or epigastric discomfort; (3) rapid growth or rupture; and (4) Kasabach-Merritt syndrome. Among the 13 patients operated on, 12 had tumours >5 cm in size. The remaining patient had a tumour 3·5 cm in diameter but was operated on because of considerable epigastric pain. Of the 20 non-surgical patients, 19 had small haemangiomas <5 cm in diameter. Although three patients were symptomatic, no specific treatment was administered because the symptoms did not pose any hazard in their daily life. Only one patient was observed with a large haemangioma of 11 cm; he refused to undergo any operation.

For patients having surgery, mortality, postoperative complications and recurrence were evaluated. Those not operated on were followed up as outpatients using ultrasonography approximately every 6 months to evaluate clinical course, tumour growth and rupture.

Results

Table 1 gives patient details. There was no significant difference in age or sex between the operated and non-operated groups. Symptoms were also similar in both groups, although in the observed patients they were less severe. Resected tumour sizes in the operated group were significantly larger than those of the non-operated group ($P<0{\cdot}01$).

Surgical patients

Figure 1 shows the clinical data on all the patients undergoing excision. Tumour size ranged from 3·5 to 15 cm. All had entirely normal preoperative liver function tests. A right lobectomy was performed in three and a left lobectomy in one. A left lateral

Table 1 *Patient details* (n = *33*)

	Operated ($n=13$)	Observed ($n=20$)
Sex ratio (male:female)	6:7	11:9
Age (years)*	50(10)	52(9)
Symptoms		
Epigastric or hypochondrial pain	2	1
Back pain	1	2
Symptoms due to other diseases	4	12
None	6	5
Tumour diameter		
<2 cm	0	9
2–5 cm	1	10
5–10 cm	9	0
>10 cm	3	1
Mean (cm)*	7·7(3·3)	2·8(2·3)†

* Values are mean(s.d.). † $P<0{\cdot}01$

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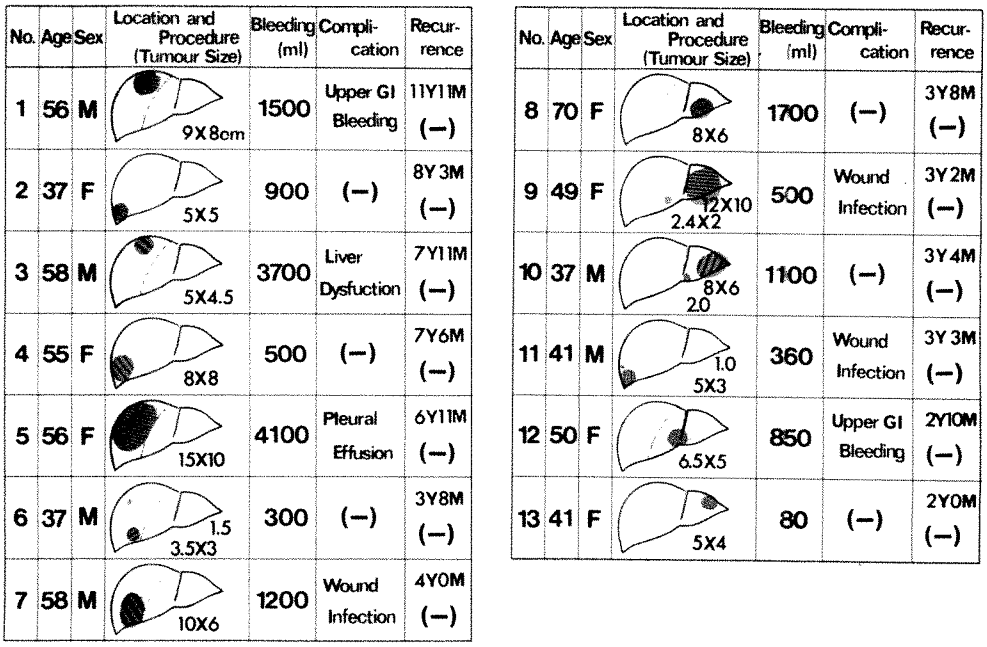

No.	Age	Sex	Location and Procedure (Tumour Size)	Bleeding (ml)	Complication	Recurrence
1	56	M	9X8cm	1500	Upper GI Bleeding	11Y11M (—)
2	37	F	5X5	900	(—)	8Y 3M (—)
3	58	M	5X4.5	3700	Liver Dysfuction	7Y11M (—)
4	55	F	8X8	500	(—)	7Y6M (—)
5	56	F	15X10	4100	Pleural Effusion	6Y11M (—)
6	37	M	1.5 3.5X3	300	(—)	3Y8M (—)
7	58	M	10X6	1200	Wound Infection	4Y0M (—)
8	70	F	8X6	1700	(—)	3Y8M (—)
9	49	F	12X10 2.4X2	500	Wound Infection	3Y 2M (—)
10	37	M	8X6 2.0	1100	(—)	3Y 4M (—)
11	41	M	1.0 5X3	360	Wound Infection	3Y 3M (—)
12	50	F	6.5X5	850	Upper GI Bleeding	2Y10M (—)
13	41	F	5X4	80	(—)	2Y0M (—)

Figure 1 *Results for the operated patients. (●) Location of tumour; ☐, region excised. Three patients had symptoms: case 2, right back pain; case 3, right hypochondrial pain; case 6, epigastric pain. GI, gastrointestinal; Y, years; M, months*

Table 2 *Tumour behaviour in 20 non-surgical patients*

Tumour behaviour	Tumour size < 2 cm ($n = 9$)	 2–5 cm ($n = 10$)	 ≥ 5 cm ($n = 1$)
Enlargement	0	0	0
No change in size	7	10	1
Decrease in size	2	0	0

segmentectomy was undertaken in three patients, and the others had either a subsegment or less resected. Three had some symptoms, all of which were relieved after resection.

Intraoperative bleeding ranged from 80 to 4100 ml. Complications after operation included two cases of upper gastrointestinal tract bleeding, one liver dysfunction and other minor problems such as wound infection or pleural effusion. No death occurred after operation.

None of the patients had any recurrent haemangioma during the period of follow-up, which ranged from 2 years to 11 years 10 months. Two patients (cases 6 and 8) had residual tumour. In both, no notable change in tumour size was observed over 3 years 8 months and 3 years 2 months, respectively.

Non-surgical patients

These 20 patients were divided into three groups according to tumour size, as shown in *Table 2*. The first group had a tumour size < 2 cm, the second group 2–5 cm, and the third group ≥ 5 cm. During the follow-up period of 18 months to 8 years (mean 3 years 11 months), two tumours decreased in size. No enlargement or rupture of the lesions was observed. In addition, no patients demonstrated any progression of their symptoms.

Case report

A 54-year-old man was discovered by chance to have a huge hyperechoic mass in his liver on ultrasonography (*Figure 2a*). Hepatic angiography showed a mass lesion, 11 × 10 cm in size, including irregular patchy poolings in the right lobe of liver (*Figure 2b*). No abnormality was recognized from liver function tests. He did not consent to have a resection and has been under observation since then. Four and a half years later ultrasonography showed no enlargement of the tumour (*Figure 2c*).

Discussion

Cavernous haemangioma is a benign tumour of the liver; however, it is frequently excised[1,2,5,6,9]. The optimum clinical management of haemangioma still remains controversial[1,2,7,9]. In the 13 patients operated on in this series, there was no evidence of recurrence of haemangioma, and all were able to lead ordinary lives. Two small haemangiomas which were left in the liver did not change in size. In addition, no operative deaths or severe postoperative complications occurred in these 13 patients. In most series previously reported[6,9], there have also been no deaths, except in emergency cases due to spontaneous bleeding. Schwartz and Husse[9] reported a complication rate of 18–31 per cent; it was 23 per cent in our experience with regard to major complications. Previous reports have indicated a rate of postoperative complications of about 40 per cent after hepatectomy for hepatocellular carcinoma[10,11]. In cases without cirrhosis, Choi *et al.* reported a morbidity rate of 15 per cent[11]. In this department, the morbidity rate after hepatectomy for hepatocellular carcinoma was 24 per cent from 1985 to 1988[12]. Thus, it may be concluded that surgical excision for haemangioma is as safe as for other diseases of the liver. Therefore such tumours may, if necessary, be excised, unless the risks are deemed overwhelming due to some systemic disease or because of anatomical considerations[2]. In some instances, however, other treatments, such as radiotherapy, arterial ligation or embolization, may be effective[8,13].

In the present series, 95 per cent of tumours were < 5 cm in size and showed no enlargement or rupture; no progression of symptoms was recorded. These results suggest that haemangiomas < 5 cm in diameter need not be excised but should instead be periodically surveyed. Since small hepatocellular carcinomas may have fatty deposits which give a hyperechoic appearance on ultrasonography, making them difficult to distinguish from haemangioma, diagnostic angiography and surgical excision should not be withheld in such indefinite cases, even when tumours are not located on the surfaces of the liver. Recent improvements, however, in magnetic resonance imaging have greatly contributed to the tumours[14]. Therefore, the indication for diagnostic angiography and surgery in such small tumour cases should become progressively restricted in the future.

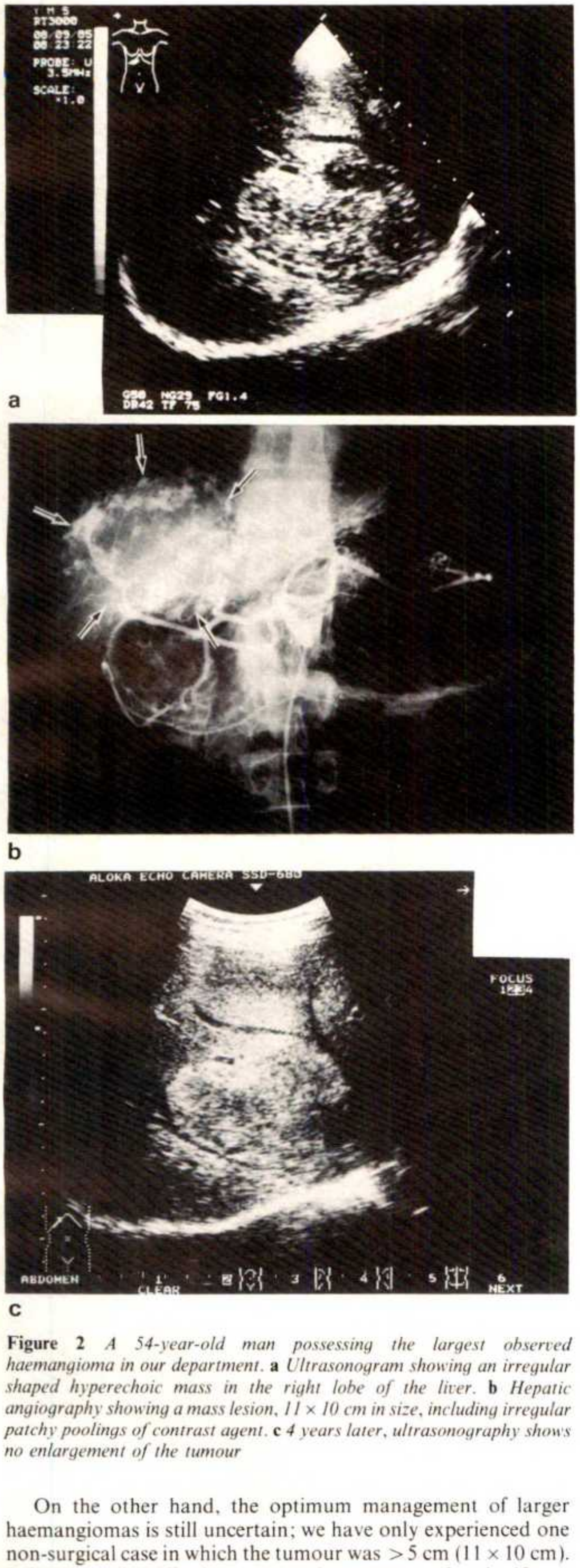

Figure 2 *A 54-year-old man possessing the largest observed haemangioma in our department.* **a** *Ultrasonogram showing an irregular shaped hyperechoic mass in the right lobe of the liver.* **b** *Hepatic angiography showing a mass lesion, 11 × 10 cm in size, including irregular patchy poolings of contrast agent.* **c** *4 years later, ultrasonography shows no enlargement of the tumour*

On the other hand, the optimum management of larger haemangiomas is still uncertain; we have only experienced one non-surgical case in which the tumour was >5 cm (11×10 cm). It is extremely difficult to prove the presence of a significant risk in larger haemangiomas. Such proof can only be achieved by long-term observation of larger lesions. Perhaps in patients with a large lesion who are unable to undergo excision for some reason, such as related systemic disease, a lengthier follow-up accurate diagnostic distinction between haemangioma and hepatocellular carcinoma, especially in solitary small liver may shed some light on this problem. In the present series the haemangiomas in 12 of the 13 cases with lesions >5 cm in size were located on the surface of the liver. In particular, five of them were in the lateral segment of the liver, which has an increased potential for exposure to trauma. In this situation, haemangiomas may be considered for resection, but size alone should not be the absolute indication for surgery.

Andersson and Bengmark[6] reviewed 22 cases of spontaneous rupture of haemangioma. Some authors reported patients with rapid growth of the haemangioma during pregnancy[4,9,15,16]. There is a possibility that pregnancy or hormonal changes influence the growth of haemangioma. In addition, Trastek *et al.*[5] reported that enlargement of cavernous haemangioma may be due to dilatation of existing channels rather than new growth. It is suggested that haemangioma is probably a congenital abnormality and not a neoplasm.

Many reports have referred to a predominance of women with this disease[6,9,17]. However, no differences in sex and age were seen in the present study. This may be partly due to current improvements in diagnostic techniques and imaging instruments, which makes discovery of small asymptomatic haemangiomas easier. It is possible that in the past symptomatic haemangiomas may have been more frequently discovered in women because of an association with hormonal change.

In conclusion, most haemangiomas <5 cm in diameter should be regularly observed if the diagnosis is secure. Tumours >5 cm in diameter can be conservatively managed unless they are symptomatic or exhibit rapid growth. When necessary, surgical treatment can be well justified due to low morbidity and no mortality.

References

1. Adam YG, Huvos AG, Fornter JG. Giant hemangiomas of the liver. *Ann Surg* 1970; **172**: 239–45.
2. Starzl TE, Koep LJ, Weil R III *et al.* Excisional treatment of cavernous hemangioma of the liver. *Ann Surg* 1980; **192**: 25–7.
3. Ochsner JL, Halpert B. Cavernous hemangioma of the liver. *Surgery* 1958; **43**: 577–82.
4. Kato M, Sugawara I, Okada A *et al.* Hemangioma of the liver: diagnosis with combined use of laparoscopy and hepatic arteriography. *Am J Surg* 1975; **129**: 698–704.
5. Trastek VF, van Heerden JA, Sheedy PF II, Adson MA. Cavernous hemangiomas of the liver: resect or observe? *Am J Surg* 1983; **145**: 49–53.
6. Andersson R, Bengmark S. Surgical treatment of cavernous hemangioma of the liver. *Acta Chir Scand* 1988; **154**: 577–9.
7. Sinanan MN, Marchioro T. Management of cavernous hemangioma of the liver. *Am J Surg* 1989; **157**: 519–22.
8. Takagi H, Kido C, Morimoto T, Yasue M, Kato H. Surgical treatment of cavernous hemangioma of the liver. *J Surg Oncol* 1984; **24**: 91–9.
9. Schwartz SI, Husse WC. Cavernous hemangioma of the liver: a single institution report of 16 resections. *Ann Surg* 1987; **205**: 456–65.
10. Tsuzuki T, Sugioka A, Ueda M *et al.* Hepatic resection for hepatocellular carcinoma. *Surgery* 1990; **107**: 511–20.
11. Choi TK, Lai Edward CS, Fan ST, Mok Francis PT, Wong J. Results of surgical resection for hepatocellular carcinoma. *Hepatogastroenterology* 1990; **37**: 172–5.
12. Matsumata T, Kanematsu T, Shirabe K *et al.* Decreased morbidity and mortality rates in surgical patients with hepatocellular carcinoma. *Br J Surg* 1990; **77**: 677–80.
13. Kawarada Y, Mizumoto R. Surgical treatment of giant hemangioma of the liver. *Am J Surg* 1984; **148**: 287–91.
14. Itai Y, Ohnishi S, Ohtomo T *et al.* Hepatic cavernous hemangioma in patients at high risk for liver cancer. *Acta Radiol* 1987; **28**: 697–701.
15. Ishak KG, Robin L. Benign tumors of the liver. *Med Clin North Am* 1975; **59**: 995–1013.
16. White TT. Cavernous hemangiomas of the liver: resect or observe? *Am J Surg* 1983; **145**: 52–3 (Discussion).
17. Goodman ZD. Benign tumors of the liver. In: Okuda K, Ishak KG, eds. *Neoplasms of the Liver*. Japan: Springer-Verlag, 1987: 105–25.

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Operative choledochoscopy in patients with acute cholangitis: a prospective, randomized study

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A prospective, randomized evaluation of operative choledochoscopy was carried out during emergency surgery in patients with acute cholangitis or acute suppurative cholangitis when conservative management had failed. After common bile duct exploration, 79 patients were randomized to have choledochoscopy and 78 patients to the control group. Laboratory and clinical parameters showed that choledochoscopy did not increase the incidence of septicaemia, acute pancreatitis, persistent cholangitis, postoperative wound sepsis, intraperitoneal sepsis and hospital mortality. The incidence of retained common bile duct stones detected by T tube cholangiography performed in the second postoperative week was significantly reduced ($P < 0.01$) after choledochoscopy. Choledochoscopy detected stones missed by conventional common bile duct exploration in ten patients. It is concluded that choledochoscopy is a safe and effective technique in patients with acute cholangitis and acute suppurative cholangitis.

Operative choledochoscopy is widely accepted by surgeons in elective exploration of the common bile duct because direct inspection of the biliary tree reduces the risk of residual stones, uncovers occult pathological lesions and identifies filling defects on operative cholangiograms and anatomical abnormalities in the biliary tree[1]. Biopsy can be performed and impacted stones removed[2,3]. In patients with acute cholangitis its place is less well defined as biliary tract infection makes the procedure potentially more dangerous. Theoretical risks are increased incidence of septicaemia due to cholangiovenous reflux of infected bile under high pressure[4,5], worsening of cholangitis owing to reflux of infected bile[6], precipitation of attacks of acute pancreatitis from reflux of infected bile into the pancreatic duct[7,8], increased incidence of postoperative intraperitoneal and wound sepsis owing to leakage of infected bile and irrigation fluid around the choledochoscope, and likelihood of iatrogenic injury to the infected biliary tree due to tissue congestion, hyperaemia and increased tissue friability[6]. The incidence of retained common bile duct stones may be higher than in elective operations since choledochoscopic views may be impaired because of the presence of turbid infected bile, tissue oedema and congestion and inflammatory webs. We have demonstrated that operative choledochoscopy is effective and safe in a prospective study of 70 patients with acute cholangitis and acute suppurative cholangitis[6], but are uncertain whether the benefits obtained with choledochoscopy are more than offset by the increased risks of surgical complications.

Patients and methods

Patient selection

A multicentre study was carried out involving the Government Surgical Unit at the Queen Mary Hospital, the Surgical C Unit at the Queen Elizabeth Hospital, and the Department of Surgery at the Prince of Wales Hospital. Emergency endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic biliary drainage (EBD) were available for 24 h only in the last centre.

All patients admitted into these departments between 1984 and 1990 who required emergency surgery for acute cholangitis or acute suppurative cholangitis were considered for participation in this study.

Study design

All patients with a clinical diagnosis of acute cholangitis were treated initially with conservative management: nasogastric aspiration, intravenous fluid, systemic antibiotics and close observation. Investigations included haemoglobin, total leucocyte and differential counts, liver and renal function tests, plain abdominal radiography and ultrasonography of the hepatobiliary system. Patients who responded to conservative management underwent diagnostic ERCP when the biliary tract infection was controlled. Those who failed to respond and those who deteriorated underwent biliary drainage. The indications for emergency biliary drainage were: (1) unrelenting cholangitis with high swinging fever and significant abdominal signs; (2) failure to respond to various courses of antibiotics; (3) cholangitis with septicaemia; (4) impending septicaemic shock with rising pulse rate and falling blood pressure; and (5) septicaemic shock. Emergency biliary drainage was carried out surgically for the patients in the departments without emergency ERCP and EBD. This was performed endoscopically in the department where this service was available. Patients with failed EBD underwent surgical drainage.

Patients received 2 g cefoperazone intravenously before operation and the antibiotic was continued at a dosage of 1 g 6-hourly for 7 days after operation. At laparotomy the common bile duct was identified and an operative cholangiogram carried out by needle puncture of the common bile duct to confirm the presence of biliary stones and to rule out other pathologies causing the cholangitis. Bile was taken for microscopy and culture. Care was taken not to overfill the biliary tree with contrast by aspirating the bile before injection of a small amount of contrast into the biliary system to avoid cholangiovenous reflux and septicaemia. The duct was explored through a longitudinal supraduodenal choledochotomy and cleared of stones in the standard way.

Patients were then randomly allocated to undergo choledochoscopy or not. Excluded from this study were patients with: (1) intrahepatic stones; (2) acute obstructive suppurative cholangitis[9,10] with profound septicaemic shock; and (3) life-threatening associated medical diseases. In the last two groups of patients, it was considered unethical to prolong the operation time and to introduce additional surgical risks by performing choledochoscopy. Patients with transient septicaemic shock responding to preoperative resuscitation were included.

Choledochoscopy was carried out with the stay stitches crossed over a rigid Storz choledochoscope (Karl Storz GmbH, Tuttlingen, Germany). The irrigating fluid was warm normal saline in a plastic container placed within a pressure cuff inflated to 300 mmHg suspended 1 m above the patient. Retained stones were removed and choledochoscopy repeated until the duct was clear.

In both groups, the common bile duct was closed around a T tube. A tube drain to the right subhepatic space and the T tube were brought out through separate stab incisions. The wound was closed with absorbable sutures for the peritoneum and nylon for the abdominal muscles and skin.

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Table 1 *Patient details*

	Choledochoscopy ($n=79$)	Control ($n=78$)
Sex ratio (male:female)	38:41	36:42
Age (years)*	65·4(13·3)	65·1(12·8)
No previous biliary operation	70	68
Positive common bile duct bile culture	69	71
Associated medical diseases	8	7

* Values are mean(s.d.)

Additional investigatory procedures

Septicaemia. Blood for aerobic and anaerobic cultures was taken before and after operation and whenever patients had chills, rigors or fever over 39·5°C.

Persistent cholangitis. The durations of postoperative pyrexia and hospital stay were recorded. Liver function tests were determined before and at 3-day intervals after operation.

Bile cultures. Aerobic and anaerobic cultures were taken without delay for common bile duct bile.

Acute pancreatitis. Serum amylase levels were determined before and after operation. A level of over 900 units/l was diagnostic of acute pancreatitis.

Aspects of choledochoscopy. The operating surgeon completed a proforma giving details of completeness of the examination (duodenal mucosa to right and left hepatic ducts, adequacy of view, possible injuries, whether overlooked stones were detected and whether these could be removed endoscopically). The time spent in choledochoscopy was recorded, but excluded the time taken to remove impacted stones.

Retained common bile duct stones. Retained common bile duct stones were detected in T tube cholangiograms performed in the second postoperative week.

Definition of wound and intraperitoneal sepsis

Patients were reviewed at 2 and 6 weeks after discharge from hospital and then 3-monthly for at least 1 year.

The criteria of Ljungqvist were used to determine whether the wounds were infected or clean[11]. Wound infection was defined as a wound with purulent discharge. Wounds with serous discharge which gave positive bacteriological cultures and wounds with serous discharge after the patients had returned home (without culture) were included in the infected group.

Intraperitoneal abscess was diagnosed ultrasonographically or by laparotomy.

Estimated sample size

Reports[2,7,12–20] on the incidence of retained common bile duct stones using a choledochoscope (with few exceptions[21–23]) cite 0–3 per cent. Without choledochoscopy the incidence was 10–27 per cent[14,24]. Accepting an α risk of 0·05 and a β risk of 0·10, inclusion of 160 patients into the study (number rounded up to next 10 patients) would show a statistically significant difference in the retained common bile duct stone rate between the two groups.

Statistical analysis

Student's t test or the χ^2 with Yates' correction were employed for statistical evaluation. Data were considered to be significant when $P<0{\cdot}05$.

Results

Pre-randomization exclusions

We excluded all patients with acute cholangitis who responded to the initial conservative treatment in all three centres (86 per cent), and those patients who had a successful EBD where this emergency service was available (85 per cent of attempted EBD). Of 194 patients, 34 who underwent emergency biliary surgery were excluded from the study and included 19 patients with intrahepatic stones, eight patients with profound septicaemic shock and seven patients with life-threatening associated medical diseases (four with heart failure, two with very poor pulmonary reserve and one with chronic renal failure). Six of 15 of the last two groups of high-risk patients died soon after surgery.

Post-randomization withdrawals

Three patients were withdrawn after randomization because of protocol violations. One patient (choledochoscopy group) had dislodgement of the T tube before cholangiography and two (controls) because of the use of intraoperative postexploratory cholangiogram in one and because the surgeon proceeded to a choledochoduodenostomy at the end of the operation in the other.

Matching of groups

Of the 157 evaluable patients, 79 were in the choledochoscopy group and 78 in the control group. The randomized groups were well matched with respect to patient characteristics (*Table 1*).

Operative results (Table 2)

Septicaemia. There was no statistical difference between the number of patients with positive preoperative and postoperative blood cultures in the groups. All patients with positive postoperative blood cultures had positive preoperative cultures and the same organisms were isolated, suggesting that the persistent septicaemia was the result of cholangitis and not related to common bile duct exploration with or without choledochoscopy.

Acute pancreatitis. There was no statistical difference between the incidence of preoperative or postoperative pancreatitis in the two groups. No patient with a normal preoperative serum amylase had clinical or biochemical evidence of acute pancreatitis after operation.

Persistent cholangitis. There were no statistically significant differences in the duration of postoperative pyrexia or hospital stay. No patient had persistent fever and abnormal liver function tests suggesting persistent cholangitis.

Wound and intraperitoneal sepsis. There was no difference in the incidence of wound and intraperitoneal sepsis between the two groups.

Hospital mortality. Three patients died from septicaemia after operation, two in the choledochoscopy group and one in the control group.

Table 2 *Operative results*

	Choledochoscopy ($n=79$)	Control ($n=78$)
Positive blood culture		
Before operation	35	37
After operation	11	9
Raised serum amylase level†		
Before operation	4	3
After operation	3	3
Postoperative pyrexia (days)*	3·3(2·4)	3·2(2·7)
Hospital stay (days)*	9·9(4·8)	12·1(5·6)
Persistent cholangitis	0	0
Wound infection		
Deep	6	5
Superficial	2	1
Intraperitoneal sepsis	1	0
Hospital mortality	2	1
Retained common bile duct stones	1	13

* Values are mean(s.d.). † Increase by a factor of seven or greater

Incidence of retained common bile duct stones. Patients in the control group had significantly higher incidence of retained common bile duct stones (χ^2 with Yates' correction = 0·64, $P < 0·01$).

Aspects of choledochoscopy. Choledochoscopy helped detect stones in the common bile duct missed by conventional exploration in ten patients. There were no inadvertent injuries to the biliary tree and choledochoscopic views were satisfactory in all patients. The time spent in choledochoscopy (mean(s.d.)) was 13·1(4·7) min.

Bacterial cultures

Cultures from common bile duct bile were positive in 140 patients (89·2 per cent). The common aerobes isolated, either in pure or mixed growth, were *Escherichia coli* in 95 patients (60·5 per cent), *Klebsiella* spp. in 24 patients (15·3 per cent), *Streptococcus faecalis* in 18 patients (11·5 per cent) and *Proteus* spp. in 11 patients (7 per cent). The common anaerobes isolated were *Bacteroides fragilis* in five patients (3·2 per cent) and *Clostridium welchii* in two patients (1·3 per cent). Anaerobes were found only in patients who had previous biliary tract surgery or in patients with gangrenous cholecystitis.

The common organisms isolated from blood or infected wounds were *E. coli*, *Klebsiella* spp. and *S. faecalis*. No anaerobes were isolated from blood or wound cultures.

Retained common bile duct stones

Fourteen patients had retained common bile duct stones which passed spontaneously in five, while nine had retained stones removed through the T tube tract.

Discussion

Initial conservative management of patients with acute cholangitis will allow the majority to resolve[25]. When sepsis progresses, biliary decompression becomes mandatory. Recent results using non-operative measures such as percutaneous biliary drainage established with transhepatic catheters[9,26,27] have been good. After endoscopic papillotomy followed by active instrumental stone extraction[28,29] or introduction of a nasobiliary catheter[30], successful decompression of the infected biliary system has been reported with resolution of sepsis within 24 h and amelioration of jaundice. The routine use of such non-operative measures in emergency situations has the following limitations: (1) success is dependent on local experience and expertise; (2) complications may follow and cholecystectomy may be required later; (3) when these procedures fail, biliary decompression is delayed[31]; and (4) the availability of 24-h emergency service of non-operative procedures is not universal.

Retained common bile duct stones represent a significant source of morbidity after choledocholithotomy. Improved methods of retrieval and dissolution are available[3], but the cost and potential complications mandate the adoption of the most effective methods for complete stone removal at initial surgery. Conventional techniques of exploration of the common bile duct include palpation alone and some use postexploratory cholangiography but it is often omitted[13] and stones can easily be overlooked[32].

Intraoperative choledochoscopy offers advantages, not least of which are efficacy and safety[1,2,7,12–23]. In the collected series reviewed by Gartell and McGinn[7], the incidence of retained common bile duct stones, with few exceptions[21–23], was 0·3 per cent. There was no significant difference between flexible and rigid choledochoscopes[2] although the view with the rigid instrument is reported to be less extensive[1,33].

This randomized trial confirms that choledochoscopy is valuable in the reduction of retained common bile duct stones. It is safe to use in acute cholangitis and acute suppurative cholangitis, and should be carried out when the patient's general condition is reasonably stable. It is, however, questionable whether choledochoscopy should be performed in patients with acute obstructive suppurative cholangitis[9,10], patients with serious associated medical diseases, or patients in poor general conditions[1]. Choledochoscopy in these patients may prolong the operation time and may increase the operative mortality. In these patients decompression of the infected and obstructed biliary tree by operative or non-operative measures is required and any common bile duct stones may be dealt with by stone retrieval, stone dissolution or surgery, when the patient's condition improves[1,12].

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References

1. Lau WY, Fan ST, Yip WC, Poon GP, Wong KK. Optimal irrigation pressures in operative choledochoscopy. *Aust NZ J Surg* 1988; **58**: 63–6.
2. Leslie D. Endoscopy of the bile duct. An evaluation. *Aust NZ J Surg* 1974; **44**: 340–2.
3. Jordan GL Jr. Choledocholithiasis. *Curr Probl Surg* 1982; **19**: 722–98.
4. Dellinger EP, Kirshenbaum G, Weinstein M, Steer M. Determinants of adverse reaction following T-tube cholangiogram. *Ann Surg* 1980; **191**: 397–403.
5. Hultborn A, Jacobsson B, Rosengren B. Cholangiovenous reflux during cholangiography. *Acta Chir Scand* 1962; **123**: 111–24.
6. Lau WY, Chong KK, Fan ST *et al.* A scientific evaluation of operative choledochoscopy in acute cholangitis. *Ann Surg* 1987; **206**: 142–7.
7. Gartell PC, McGinn FP. Choledochoscopy: are stones missed? A controlled study. *Br J Surg* 1984; **71**: 767–9.
8. Berci G, Shore G, Morgrentern L, Hamlin JA. Choledochoscopy and operative fluorocholangiography in the prevention of retained bile duct stones. *World J Surg* 1978; **2**: 411–27.
9. Kinoscita H, Hirohashi K, Igawa S *et al.* Cholangitis. *World J Surg* 1984; **8**: 963–9.
10. Boey JH, Way LW. Acute cholangitis. *Ann Surg* 1980; **191**: 264–70.
11. Ljungqvist U. Wound sepsis after clean operations. *Lancet* 1964; **i**: 1095–7.
12. Nora PF, Berci G, Dorazio RA *et al.* Operative choledochoscopy. Results of a prospective study in several institutions. *Am J Surg* 1977; **133**: 105–10.
13. Ashby BS. Operative choledochoscopy in common bile duct surgery. *Ann R Coll Surg Engl* 1985; **67**: 279–83.
14. Bauer JJ, Salky BA, Gelernt IM, Kreel I. Experience with the flexible fiberoptic choledochoscope. *Ann Surg* 1981; **194**: 161–6.
15. Escat J, Glucksman DL, Maigne C *et al.* Choledochoscopy in surgery for choledocholithiasis. Six year experience in 380 consecutive patients. *Am J Surg* 1984; **147**: 670–1.
16. Kappes SK, Adams MB, Wilson SD. Intraoperative biliary endoscopy. Mandatory for all common duct operations? *Arch Surg* 1982; **117**: 603–7.
17. Keighley MRB, Kappas A. Evaluation of operative choledochoscopy. *Surg Gynecol Obstet* 1980; **150**: 357–9.
18. Finnis D, Rowntree T. Choledochoscopy in exploration of the common bile duct. *Br J Surg* 1977; **64**: 661–4.
19. Ernst D, Windsor CWO. The use of a rigid choledochoscope in exploration of the common bile duct. *Br J Surg* 1982; **69**: 463–4.
20. Motson RW, Wood AJ, DeJode LR. Operative choledochoscopy: experience with a rigid choledochoscope. *Br J Surg* 1980; **67**: 406–9.
21. Kappas A, Alexander-Williams J, Keighley MRB, Watts GT. Operative choledochoscopy. *Br J Surg* 1979; **66**: 177–97.
22. Rattner DW, Warshaw AL. Impact of choledochoscopy on the management of choledocholithiasis: experience with 499 common duct explorations at the Massachusetts General Hospital. *Ann Surg* 1981; **194**: 76–9.
23. Feliciano DV, Matton KL, Jordan GL Jr. The value of choledochoscopy in exploration of the common bile duct. *Ann Surg* 1980; **191**: 649–54.
24. Goldberg HI. Operative and postoperative cholecystocholangiography. *Semin Roentgenol* 1976; **11**: 203–11.
25. Saharia PC, Cameron JL. Clinical management of acute cholangitis. *Surg Gynecol Obstet* 1976; **142**: 369–72.

26. Gould RJ, Vogelgang RL, Neiman HL *et al.* Percutaneous biliary drainage as an initial therapy in sepsis of the biliary tract. *Surg Gynecol Obstet* 1985; **160**: 523–7.
27. Pessa ME, Hawkins IF, Vogel SB. The treatment of acute cholangitis. Percutaneous transhepatic biliary drainage before definitive therapy. *Ann Surg* 1986; **205**: 389–92.
28. Gogel HK, Runyon BA, Volpicelli NA, Palmer RC. Acute suppurative obstructive cholangitis due to stones: treatment by urgent endoscopic sphincterotomy. *Gastrointest Endosc* 1987; **33**: 210–3.
29. Leese T, Neoptolemos JP, Baker AR, Carr-Cocke DL. Management of acute cholangitis and the impact of endoscopic sphincterotomy. *Br J Surg* 1986; **73**: 988–92.
30. Ikeda S, Tanaka M, Itoh H *et al.* Emergency decompression of bile duct in acute obstructive suppurative cholangitis by duodenoscopic cannulation: a lifesaving procedure. *World J Surg* 1981; **5**: 587–93.
31. Heinerman PM, Boeckl O, Pimpl W. Selective ERCP and preoperative stone removal in bile duct surgery. *Ann Surg* 1989; **209**: 267–72.
32. Hall RC, Sakiyalak P, Kim SK *et al.* Failure of operative cholangiography to prevent 'retained' common bile duct stones. *Am J Surg* 1973; **125**: 51–63.
33. Eleftheriadis E, Zissiadis A, Kotzampassi K, Aletras H. Rigid or flexible choledochoscopy? *Endoscopy* 1985; **17**: 212–3.

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Clinical usefulness of polymorphonuclear elastase in predicting the severity of acute pancreatitis: results of a multicentre study

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The usefulness and clinical applicability of quantitative plasma polymorphonuclear elastase determinations in the diagnosis of the severity of acute pancreatitis was analysed in a multicentre study and was compared with the usual prognostic systems of Ranson and Osborne et al. *The study comprised 182 patients, 154 with a mild episode of acute pancreatitis and 28 with a severe episode, defined by the development of major complications or a fatal outcome. In the severe cases neutrophilic elastase reached significantly higher values than in mild cases* ($P < 0{\cdot}001$) *by the time the patient was admitted (2–12 h after the onset of the disease), reflecting considerable leucocyte activation. The sensitivity and specificity of this test are therefore greater than 90 per cent, with a positive severity predictive value of almost 80 per cent at the time of admission and 97 per cent after 24 h, and a negative predictive value of approximately 98 per cent. In addition to requiring 48 h for evaluation, the usual prognostic systems show a sensitivity of 77–85 per cent, a specificity of 70–77 per cent, a positive predictive value of 40–48 per cent, and a negative predictive value of 92–95 per cent, clearly lower than those obtained with leucocyte elastase. Polymorphonuclear elastase is therefore a very early and reliable marker in the diagnosis of the severity of acute pancreatitis, in addition to being easily adaptable to the routine of any hospital laboratory.*

The phagocytic mononuclear and polymorphonuclear systems are being increasingly implicated in the production of extensive tissue damage in many inflammatory diseases, and may determine the severity of the clinical course in these conditions[1–3]. The capacity of neutrophils to cause tissue damage has been linked with the great harmful potential of their lysosomal proteases, mainly elastase[4]. This harmful action is facilitated by the production by the phagocytic cell itself of oxygen-containing metabolites that cause oxidative inactivation of a series of key anti-proteases (essentially α_1-protease inhibitor)[1,5] in an extracellular environment in which there is little superoxide dismutase or catalase activity[6]. Furthermore, polymorphonuclear elastase, together with the remaining neutrophilic proteases, is capable of activating cascades of the complement, kinin, coagulation and fibrinolytic systems and arachidonic acid, which are involved in the development of multisystem failure[7–10]. This complex mechanism could account for the clinical picture of acute pancreatitis and for the high morbidity and mortality of severe episodes[11]. This attractive hypothesis led us to measure the levels of circulating polymorphonuclear elastase in patients with acute pancreatitis and to compare this test with the prognostic criteria usually used for the prediction of severity[12,13].

Materials and methods

Patients

A detailed protocol was applied prospectively to a total of 182 patients diagnosed as having acute pancreatitis over a period of 14 months. The diagnosis was based on the presence of a typical clinical picture together with elevated serum levels of total amylase, pancreatic amylase and lipase, at no less than twice the upper limit of the normal range in each case. Subsequent morphological confirmation was also required, together with a clinical course consistent with acute pancreatitis which could not be explained by any other pathological process. The time between the onset of symptoms and the patient's admission to hospital varied between 2 and 12 h.

Severity of pancreatitis was defined according to the development of one or more major local or systemic complications of the disease (*Table 1*). Local complications were diagnosed by imaging techniques (ultrasonography, computed tomography) and/or surgical findings. Because respiratory alterations which do not require any specific therapeutic management often occur in the course of acute pancreatitis, only an arterial oxygen tension below 60 mmHg (8 kPa) combined with acute changes in clinical signs or on chest radiographs was accepted for the diagnosis of respiratory insufficiency requiring specific treatment (oxygen therapy, assisted respiration, etc.). Criteria for diagnosing other local and systemic complications are those generally accepted[14].

Methods

All patients underwent the necessary investigations for the prognostic criteria of the New York group[12] and the Glasgow group[13], according to which an episode of acute pancreatitis is predicted to be severe on the basis of three or more positive criteria.

Table 1 *Major complications of acute pancreatitis considered in the definition of severe disease*

Local complications	Systemic complications
Necrosis	Shock
Haemorrhage	Sepsis
Abscess	Pulmonary insufficiency
Pseudocyst	Cardiac insufficiency
Phlegmon	Renal insufficiency
	Severe coagulopathy
	Pancreatic encephalopathy

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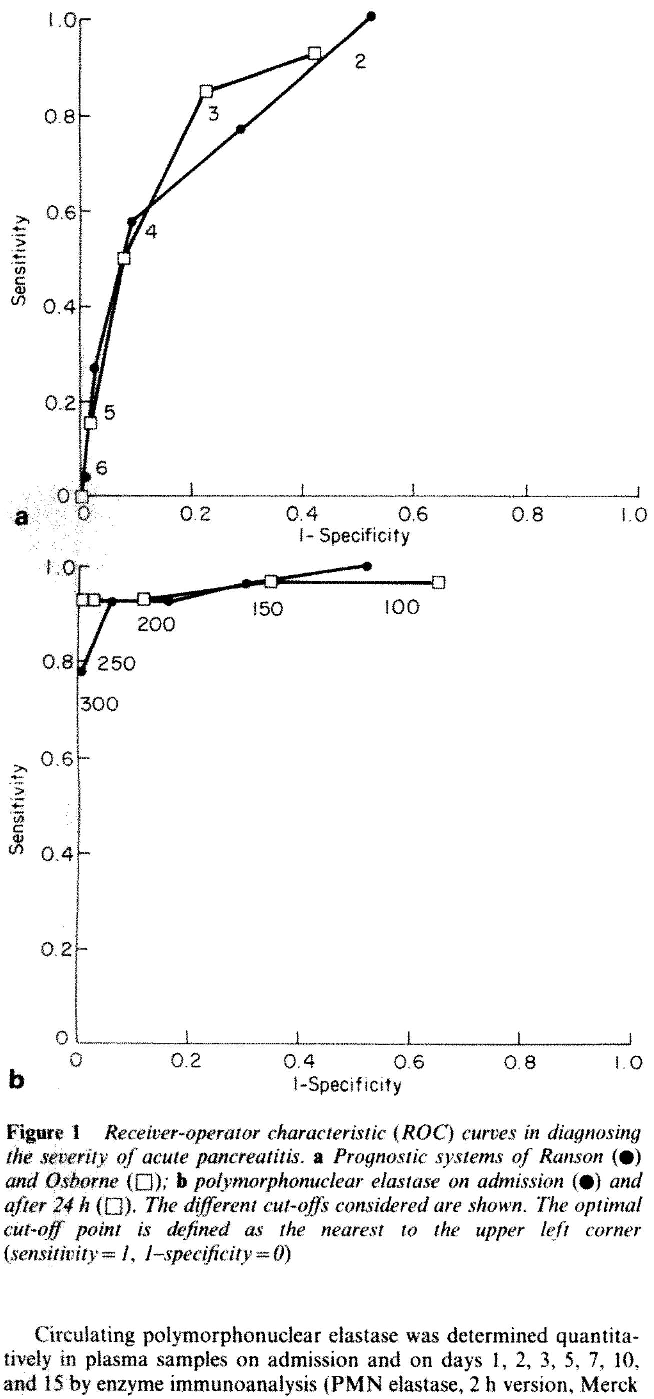

Figure 1 *Receiver-operator characteristic (ROC) curves in diagnosing the severity of acute pancreatitis.* **a** *Prognostic systems of Ranson (●) and Osborne (☐);* **b** *polymorphonuclear elastase on admission (●) and after 24 h (☐). The different cut-offs considered are shown. The optimal cut-off point is defined as the nearest to the upper left corner (sensitivity = 1, 1–specificity = 0)*

Circulating polymorphonuclear elastase was determined quantitatively in plasma samples on admission and on days 1, 2, 3, 5, 7, 10, and 15 by enzyme immunoanalysis (PMN elastase, 2 h version, Merck Immunoassay, Darmstadt, Germany). This method measures the concentration of polymorphonuclear elastase-α_1-protease inhibitor complexes. The normal range for this enzyme, calculated from the analysis of 100 blood samples from donors assumed to be healthy, is 7–43 μg/l.

Statistical analysis of the quantitative data was by Student's t-test and for the qualitative data by χ^2 test with Yates' correction in 2 × 2 contingency tables. To quantify the ability of polymorphonuclear elastase and of the multifactorial scoring systems to predict severity, sensitivity (proportion of correctly classified severe episodes), specificity (proportion of correctly classified mild episodes) and overall reliability (proportion of episodes correctly classified according to severity) were determined. The positive and negative severity predictive values were calculated by applying Bayes' theorem, using a prevalence of 0·2 of severe cases and 0·8 of mild cases, from an epidemiological study conducted in our department (unpublished work). This is a similar distribution of severity to other large series of patients who had not undergone previous selection[15,16]. Starting from the initial probability of 20 per cent that an episode of acute pancreatitis will be severe, the positive predictive value defines the probability that a patient with a positive test result will develop a severe attack while the negative predictive value quantifies the probability that a patient with a negative test result will have a mild episode (previous probability 80 per cent). Likewise the post-test odds in favour of severity (OddsF) were calculated, which indicate the probability that a patient will present with severe acute pancreatitis, taking 1 as the probability that the episode will be mild and starting from a pre-test OddsF of 0·25:1. The optimal cut-off values were calculated from the receiver-operator characteristic (ROC) curves for each test. These show the different sensitivity and specificity obtained according to the cut-off value considered to predict severity. The optimal cut-off is the value with which the test shows the best sensitivity/specificity equilibrium in the diagnosis of severity.

Results

Patient characteristics

The mean(s.d.) age of the patients was 60(18·8) years; 94 (51·6 per cent) were men and 88 (48·4 per cent) women. The distribution by aetiology showed a marked predominance of biliary pancreatitis (57·1 per cent) over alcoholic pancreatitis (17·0 per cent), mixed biliary and alcoholic cases (4·4 per cent), other forms (2·8 per cent) and idiopathic pancreatitis (18·7 per cent). Mild episodes were present in 154 patients (84·6 per cent), while the remaining 28 (15·4 per cent) had severe episodes. Overall, seven patients died (3·8 per cent of the total, 25 per cent of the severe episodes). There was no statistically significant correlation between morbidity or mortality and advanced age, sex distribution or associated aetiological factors. Sixteen patients (8·8 per cent) developed local complications, mainly pancreatic necrosis (7·1 per cent), while 26 (14·3 per cent) presented with systemic complications, mainly respiratory failure (10·4 per cent) and sepsis (9·9 per cent).

Prognostic criteria

The patients with severe episodes clearly had a larger number of positive criteria than those with mild episodes, with reference to both Ranson's system (3·7(1·20) *versus* 1·8(1·33)) and the modified Glasgow criteria (3·4(1·10) *versus* 1·5(1·31)). In both cases the difference was statistically significant ($P < 0·001$). Statistical analysis of the results obtained by progressively increasing the minimum number of criteria required for an episode of pancreatitis to be considered severe from 2–6 yielded the ROC curve shown in *Figure 1a*. This shows how optimal reliability is obtained by considering three criteria as the cut-off, agreeing with the original descriptions. The corresponding results for sensitivity, specificity, positive and negative predictive values and overall reliability obtained with these optimal cut-offs are shown in *Table 2*. The odds in favour of severity increase from a pre-test value of 0·25:1 to the post-test OddsF of 0·66:1 according to Ranson's system and to 0·92:1 according to Osborne's system. Neither of the prognostic systems showed statistically significant differences between the patients with a fatal outcome and those with the severe form who survived ($\chi^2 = 2·853$ and $\chi^2 = 2·751$, respectively).

Polymorphonuclear elastase

The plasma concentration of polymorphonuclear elastase is far higher from the time of admission in patients whose course proves to be unfavourable (severe disease), with a peak at 24 h

Table 2 *Sensitivity, specificity, positive and negative predictive values and overall reliability of the Ranson and Glasgow prognostic systems and polymorphonuclear elastase on admission and after 24 h, in the diagnosis of severity of acute pancreatitis*

	Ranson	Glasgow	Elastase on admission	Elastase at 24 h
Sensitivity	76·9	84·6	92·6	92·9
Specificity	70·3	77	94	99·3
Positive predictive value	39·6	47·9	79·4	97·1
Negative predictive value	92·4	95·2	98·1	98·2
Reliability	71·3	78·2	93·8	96·3

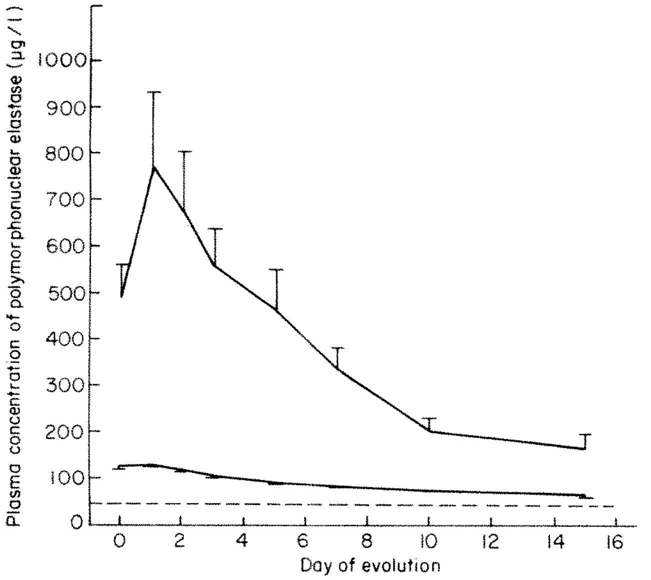

Figure 2 *Plasma concentration (mean ± s.e.m.) of polymorphonuclear elastase in patients with severe (upper line) and mild (lower line) acute pancreatitis.* – – –, *Upper normal concentration. Days 0–10,* $P<0{\cdot}001$; *day 15,* $P<0{\cdot}05$

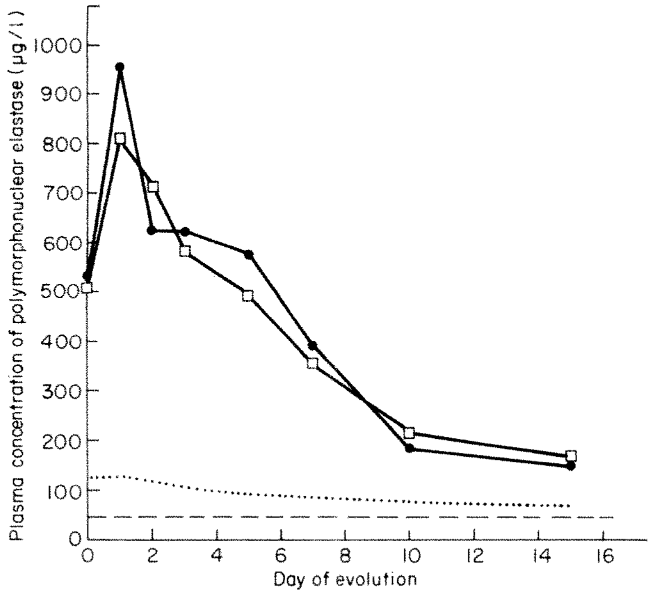

Figure 3 *Plasma concentration of polymorphonuclear elastase in patients who develop local complications* (●), *systemic complications* (☐) *and those with uncomplicated acute pancreatitis* (······). – – –, *Upper normal concentration*

(*Figures 2* and *3*). This marked difference persisted for 15 days. The ROC curves for this enzyme in predicting severity are shown in *Figure 1b*, the best reliability being obtained when 250 μg/l was taken as the cut-off on admission and 300 μg/l after 24 h. By applying these optimal cut-offs the results regarding the efficiency of the test are as shown in *Table 2* and *Figure 4*. There was an increase from pre-test OddsF of 0·25:1 to post-test OddsF of 3·86:1 on admission and to 33·18:1 on the first morning in hospital.

The course of the plasma levels of this enzyme is identical in patients who develop local complications of the disease and those who develop systemic complications (*Figure 3*). In patients with a severe attack, polymorphonuclear elastase concentrations did not reveal significantly different results in patients who died and those who survived ($t=0{\cdot}475$ on admission and $t=1{\cdot}170$ after 24 h). There was no difference in the prediction of severity of pancreatitis of biliary or alcoholic origin.

Discussion

The characteristics of the patients studied did not differ in general from those documented by other authors. The mean age of the patients was similar to that in the larger studies reported in the international literature, in which the mean age varies between 55 and 60 years[17]. In the present study, despite the greater prevalence of biliary aetiology, acute pancreatitis was not more frequent in women because of the large number of men of advanced age with biliary pathology. No increase was demonstrated in morbidity and mortality in relation to increasing age, which can probably be explained by the mild nature of the biliary pancreatitis in these patients and by the fact that no significant relationship was demonstrated between pre-existing underlying chronic diseases (diabetes, cardiovascular or respiratory disease, etc.) and the severity of the acute attack.

The application of the multifactorial prognostic criteria for the assessment of severity of pancreatitis gives a sensitivity of 85 per cent for the Glasgow criteria and 77 per cent for Ranson's criteria with specificities of 70 and 77 per cent; these results are similar to those obtained by other authors[18,19]. Starting from a 20 per cent pre-test probability, the positive predictive values of both systems are considerable, especially for the Glasgow system (48 per cent). Thus, if the pre-test OddsF are 0·25:1, a patient with three or more positive criteria has the same probability of a favourable or severe course (post-test OddsF of 0·92:1). Nevertheless, both these systems suffer from the drawback of requiring 48 h to reach a diagnosis. The efficiency of the Glasgow system is shown to be higher than that of Ranson, probably as a result of the clear predominance of episodes of biliary aetiology in the present series.

Human neutrophils are becoming increasingly accepted as mediators of tissue destruction in inflammatory diseases[1,2], based on the release of agents with considerable harmful potential, mainly oxygen-containing metabolites and proteolytic enzymes[1,2,4]. One of the earliest events in the onset of acute pancreatitis is infiltration of neutrophils and macrophages into the interstitial pancreatic space[20], which could be a fundamental stage in the development of the disease. The intensity of the response of the phagocytic cells may well determine the severity of the disease[11]. This hypothesis has been supported by our present results: the plasma concentration of polymorphonuclear elastase in patients with pancreatitis is

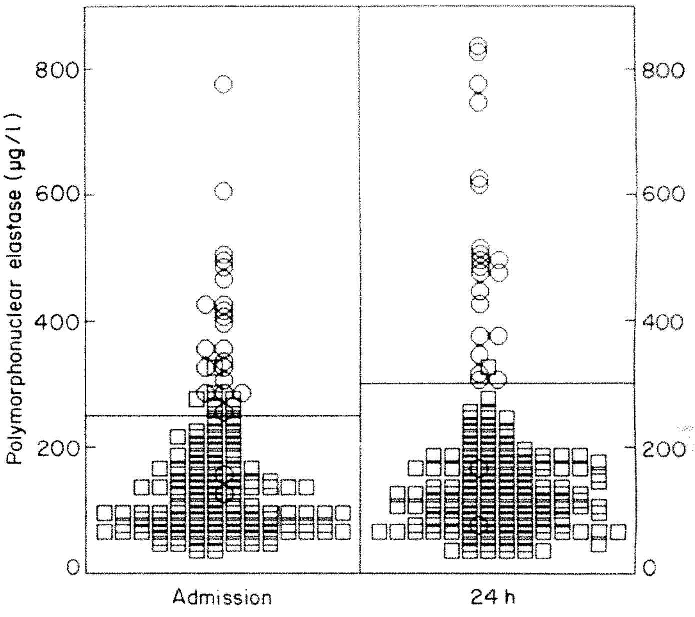

Figure 4 *Range of values and separation between mild* (☐) *and severe* (○) *acute pancreatitis related to optimal cut-off values for polymorphonuclear elastase on admission and after 24 h*

elevated a few hours after the onset of symptoms, but to a much greater extent in patients who subsequently develop a severe form of the disease. After a peak on the first morning in hospital (12–24 h after onset of disease), these patients begin to show a slow reduction in the levels of polymorphonuclear elastase, regardless of whether or not the subsequent course proves to be fatal. Significantly raised values persist up to the 15th day. It therefore appears that a conflict takes place in the interstitial pancreatic space between α_1-protease inhibitor attempting to inhibit polymorphonuclear elastase and leucocytic oxidizing agents attempting to inactivate these anti-proteases. In cases of mild pancreatitis in which the levels of elastase are moderately elevated it is possible that leucocyte material is released but in sufficiently small amounts for it to be easily inhibited by α_1-protease inhibitor (it must be taken into account that what is measured in plasma is the concentration of enzyme bound to anti-protease). In severe cases, on the other hand, the large increases in the polymorphonuclear elastase levels reflect a massive release of leucocyte material. In these cases the elastase may be able to act before being inhibited by the anti-protease, especially in the presence of the leucocytic oxidizing agents. The subsequent formation of a complex with the oxidized anti-protease would not inhibit the enzyme activity completely. In this way the whole pathophysiological process which leads to the development of severe pancreatitis could be triggered. This process precedes the development of both local and systemic complications of the disease, as can be seen from the plasma levels of the enzyme in both cases (*Figure 3*), and it is no different whether or not the outcome is fatal.

The study of the value of this enzyme in the early prognostic evaluation of pancreatitis using ROC curves shows a very special trace, with sensitivity remaining stable over a wide interval, in which the specificity gradually becomes higher. The sensitivity and specificity of this test in diagnosis of severity are very high from the time of admission (2–12 h after the onset of symptoms), clearly higher than 90 per cent. However, its most important value is the positive predictive value of severity which, starting from an initial probability of 20 per cent, reaches almost 80 per cent on admission and 97 per cent on the first morning in hospital. In this way the odds in favour of predicting severity increase from a pre-test level of 0·25:1 to almost 4:1 at the time of admission and to 33:1 after 24 h (i.e. it becomes, respectively, four and 33 times more probable that the disease will be severe if the test result is positive). In brief, the probability that a patient with acute pancreatitis with elevated levels of polymorphonuclear elastase ($>300\ \mu g/l$) will have a severe episode is very high, and such patients should therefore be closely followed up so that suitable therapeutic measures can be implemented promptly. Furthermore, the value of the test in ruling out severity is 98 per cent from the onset (negative predictive value of severity), severe acute pancreatitis occurring only exceptionally in patients with normal or only slightly elevated levels of polymorphonuclear elastase.

Uhl *et al.*[21] recently published their experience with plasma polymorphonuclear elastase levels in patients with acute and chronic pancreatitis and gastrointestinal diseases or tumours. They found a statistically significant difference in this enzyme between oedematous and necrotic episodes of acute pancreatitis ($P<0{\cdot}001$). Gross *et al.*[22] studied the value of polymorphonuclear elastase in predicting the severity of acute pancreatitis in comparison with acute phase reagents and anti-proteases; they obtained superior results by measuring the former, although they were not as demonstrative as in the present study (positive and negative predictive values of 82 and 81 per cent, respectively). However, the study by Gross *et al.* involved 75 episodes, more than half of which were severe, and the calculation of predictive values was based on this proportion, which is not representative of acute pancreatitis in the general population[15,16]. The change in the levels of polymorphonuclear elastase in particular occurs earlier compared with the change in the remaining parameters, since the synthesis of acute phase proteins in the liver is secondary to the release of interleukins 1 and 6 by macrophages and is a pathophysiological consequence of leucocyte activation[23].

To conclude, measurement of plasma polymorphonuclear elastase levels allows a very reliable prediction of the severity of an episode of acute pancreatitis at the time of admission. This supports the hypothesis of the early onset and magnitude of leucocyte activation in the course of the disease, elastase being a useful marker of the intensity of this activation. The combination of these characteristics of early onset and high diagnostic reliability, together with the simplicity of the analytical determination by the new method available, makes measurement of polymorphonuclear elastase in plasma an important advance in the clinical management of acute pancreatitis compared with the prognostic criteria used hitherto.

Acknowledgements

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References

1. Henson PM, Johnston RB Jr. Tissue injury in inflammation: oxidants, proteinases, and cationic proteins. *J Clin Invest* 1987; **79**: 669–74.
2. Malech HL, Gallin JI. Neutrophils in human diseases. *N Engl J Med* 1987; **317**: 687–94.
3. Struelens M, Dilville J, Luypaert P, Wybran J. Granulocyte elastase compared to C-reactive protein for early diagnosis of septicemia in critically ill patients. *Eur J Clin Microbiol Infect Dis* 1988; **7**: 193–5.
4. Henson PM, Henson JE, Fitlschen C, Kimani G, Bratton DL, Riches DWH. Phagocytic cells: degranulation and secretion. In: Gallin JI, Goldstein IM, Snyderman R, eds. *Inflammation: Basic Principles and Clinical Correlates*. New York: Raven Press, 1988: 363–80.
5. Weiss SJ, Curnutte JT, Regiani S. Neutrophil-mediated solubilization of the subendothelial matrix: oxidative and nonoxidative mechanisms of proteolysis used by normal and chronic granulomatous disease phagocytes. *J Immunol* 1986; **136**: 636–41.
6. Cross CE, Hallowell B, Borish ET *et al.* Oxygen radicals and human disease. *Ann Intern Med* 1987; **107**: 526–45.
7. Takaki A, Enfield DL, Thompson AR. Cleavage and inactivation of factor IX by granulocyte elastase. *J Clin Invest* 1983; **72**: 1706–15.
8. Brower MS, Harpel PC. Proteolytic cleavage and inactivation of alpha-2-plasmin inhibitor and C1 inactivator by human polymorphonuclear leukocyte elastase. *J Biol Chem* 1982; **257**: 9849–54.
9. Carlo JR, Spitznagel JK, Studer EJ, Conrad DH, Ruddy S. Cleavage of membrane bound C3bi, an intermediate of the third component of complement, to C3c and C3d-like fragments by crude leukocyte lysosomal lysates and purified leukocyte elastase. *Immunology* 1981; **44**: 381–91.
10. Lasson A, Ohlsson K. Acute pancreatitis. The correlation between clinical course, protease inhibitors and complement and kinin activation. *Scand J Gastroenterol* 1984; **19**: 707–10.
11. Rinderknecht H. Fatal pancreatitis, a consequence of excessive leukocyte stimulation? *Int J Pancreatol* 1988; **3**: 105–12.
12. Ranson JHC, Pasternack BS. Statistical methods for quantifying the severity of clinical acute pancreatitis. *J Surg Res* 1977; **22**: 79–91.
13. Osborne DH, Imrie CW, Carter DC. Biliary surgery in the same admission for gallstone-associated acute pancreatitis. *Br J Surg* 1981; **68**: 758–61.
14. Glazer G. Classification and definitions in acute and chronic pancreatitis. In: Glazer G, Ranson JHC, eds. *Acute Pancreatitis. Experimental and Clinical Aspects of Pathogenesis and Management*. London: Baillière Tindall, 1988: 37–50.
15. Goebell H, Ammann RW, Herfarth C *et al.* A double-blind trial of synthetic salmon calcitonin in the treatment of acute pancreatitis. *Scand J Gastroenterol* 1979; **14**: 881–9.
16. Trapnell JE. The natural history and management of acute pancreatitis. *Clin Gastroenterol* 1972; **1**: 147–66.

17. Glazer G. Contentious issues in acute pancreatitis. In: Glazer G, Ranson JHC, eds. *Acute Pancreatitis. Experimental and Clinical Aspects of Pathogenesis and Management*. London: Baillière Tindall, 1988: 1–36.
18. Corfield AP, Cooper HJ, Williamson RCN *et al.* Prediction of severity in acute pancreatitis: prospective comparison of three prognosticating indices. *Lancet* 1985; **ii**: 403–7.
19. Leese T, Shaw D. Comparison of three Glasgow multifactor prognostic scoring systems in acute pancreatitis. *Br J Surg* 1988; **75**: 460–2.
20. Sanfey H, Bulkley GB, Cameron JL. The role of oxygen derived free radicals in the pathogenesis of acute pancreatitis. *Ann Surg* 1984; **200**: 405–13.
21. Uhl W, Büchler M, Malfertheiner P, Martini M, Beger HG. PMN elastase: a new serum marker for the staging of acute pancreatitis. *Digestion* 1989; **43**: 176–7.
22. Gross V, Schölmerich J, Leser HG *et al.* Granulocyte elastase in assessment of severity of acute pancreatitis. Comparison with acute-phase proteins C-reactive protein, α_1-antitrypsin, and protease inhibitor α_2-macroglobulin. *Dig Dis Sci* 1990; **35**: 97–105.
23. Helle M, Brakenhoff JPJ, De Groot ER, Aarden LA. Interleukin 6 is involved in interleukin 1-induced activities. *Eur J Immunol* 1988; **18**: 957–9.

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Pancreatic tissue and ductal pressures in chronic pancreatitis

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To assess the contribution of parenchymal hypertension to pain, pancreatic tissue pressures were measured intraoperatively in 17 patients with chronic pancreatitis and in four other patients undergoing pancreatic surgery (reference group). The technique involved direct fine needle cannulation of the pancreas using a flow infusion system, which measured parenchymal resistance to this infusion. Three to six recordings were obtained at each site. In chronic pancreatitis the pressure (mean ±s.e.m.) was substantially elevated in all regions of the pancreas compared with reference subjects: head (257±59 versus *19±5 mmHg,* $P<0.05$*); body (201±51* versus *13±6 mmHg,* $P<0.05$*) and tail (161±45* versus *11±3 mmHg,* $P<0.05$*). Elevation was greater in areas of calcific disease (281–383 mmHg) than in non-calcific disease (81–120 mmHg,* $P<0.05$*). Mean pancreatic ductal pressure in 10 patients (seven with calcific disease) was 20±4 mmHg. Differential pressure measurements within the pancreas helped determine the extent of resection in six patients with diffuse disease. The greatly increased tissue pressures in chronic pancreatitis, especially in the presence of calcification, suggest a possible 'compartment syndrome'.*

Operations for chronic pancreatitis are usually undertaken to relieve severe and crippling pain that has not responded to conservative measures such as strong analgesic drugs (including opiates) or coeliac plexus block[1]. The cause of this pain is imperfectly understood but is likely to be related to two groups of factors; those associated with the inflammatory process and those associated with the mechanical effects of pancreatic hypertension. Inflammation could cause stretching of the capsule and direct stimulation of sensory nerves within the pancreas and in the adjacent tissues; severe peripancreatitis is a notable feature at operation in patients with end-stage disease.

Ductal hypertension has frequently been reported in patients with painful chronic pancreatitis[2–5]. It provides a logical reason for draining the dilated duct in such cases. Normal pancreatic ductal pressure, as measured endoscopically or intraoperatively, is 10–15 mmHg. Values in the range of 30 to 50 mmHg have been reported in chronic pancreatitis[2,3], but it is debatable whether such modest ductal hypertension could cause severe pain. On-table pancreatography shows that ductal strictures are seldom tight in patients with duct ectasia, and relatively free flow of contrast to the duodenum is always seen after needling of a dilated duct in the body of the gland[6]. Recent work from Denmark has suggested that decompression of the pancreatic parenchyma may contribute to the analgesic effects of longitudinal pancreaticojejunostomy[7,8]. Pancreatic tissue pressure was increased in chronic pancreatitis and returned to normal after pancreatic drainage procedures that successfully relieved pain.

A flow infusion system has been used to measure pancreatic tissue pressure at various sites in 17 patients receiving surgical intervention for severe chronic pancreatitis.

Materials and methods

Pancreatic tissue and ductal pressures were measured in 17 patients with chronic pancreatitis undergoing operation for severe intractable pain between January and September 1990. Pancreatic tissue pressure was measured at various sites in the pancreas including the head, neck, body and tail, but not all patients had a complete set of recordings. Pancreatic ductal presssures were measured at different sites in ten of these patients.

There were 13 men and four women in the study, with a mean age of 40·1 years. Alcohol was the aetiological agent in 15 cases. Two patients, including one with choledochal cyst, had severe chronic pancreatitis related to previous acute inflammatory episodes. Operative procedures comprised pancreatic resection in 15 patients (proximal nine, distal six), longitudinal pancreaticojejunostomy in one patient and transduodenal pancreatic sphincteroplasty in one patient with recurrent acute attacks (but with clear cut pancreatographic evidence of chronic pancreatitis).

Suitable controls were difficult to obtain because of ethical constraints in multiple needling of a normal pancreas. Pancreatic tissue pressure was measured in four patients with none of the typical clinical, radiological or operative features of chronic pancreatitis. This reference group consisted of two men and two women, with a mean age of 42·7 years. Two patients underwent distal resection for small non-obstructing pancreatic tumours. A third, with suspected chronic pancreatitis, proved to have minimal disease following a limited distal resection. The fourth patient underwent sphincteroplasty for recurrent acute pancreatitis but had no findings at operation to suggest permanent structural damage to the pancreas.

Pancreatic tissue pressure was measured intraoperatively before any surgical manipulation of the gland (apart from that required to gain exposure) and before proceeding to operative pancreatography. The technique involved direct fine needle cannulation of the pancreatic parenchyma with measurement of the resistance to infusion. The 23-gauge needle was connected via a low-compliance continuous pneumohydraulic capillary infusion system (0·5 ml/min) to a signal amplifier and chart recorder (Beckman Dynograph R611, Beckman Instruments Incorporated, Schiller Park, Illinois, USA). The apparatus was calibrated to read zero with the tip of the fine needle exposed to air at the level of the pancreas. Three-to-six recordings were made at each site, and sampling was continued until steady values were obtained. Inadvertent needling of a blood vessel or pancreatic duct was usually obvious because of escape of the relevant fluid and measurement of a lower pressure than the surrounding diseased parenchyma. Pancreatic ductal pressure was similarly obtained in 10 patients by direct ductal cannulation as evidenced by efflux of pancreatic juice on withdrawal of the fine needle. Pancreatic pressures were expressed in mmHg (mean ±s.e.m.).

Manometric values in different parts of the pancreas were correlated with preoperative computed tomography (CT) findings and with gross assessment at laparotomy. Ten of 17 patients with chronic pancreatitis had calcification detected on CT scan, and in these both calcific and non-calcific areas were needled for measurement of pancreatic tissue pressure. Non-calcific chronic pancreatitis was defined as areas of the gland that appeared enlarged or irregular on CT scanning and/or felt indurated at operation.

The Wilcoxon two-sample test was used for statistical analysis.

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Table 1 *Pancreatic tissue pressures (mmHg) in chronic pancreatitis (mean ± s.e.m.)*

	Head	Body	Tail
Reference group	19 ± 5 (4)	13 ± 6 (4)	11 ± 3 (4)
All chronic pancreatitis	257 ± 59 (15)†	201 ± 51 (14)†	161 ± 45 (15)*
Calcific areas	383 ± 69 (8)†	348 ± 82 (5)†	281 ± 78 (6)*
Non-calcific areas	112 ± 48 (7)§	120 ± 34 (9)$^{*+}$	81 ± 23 (9)$^{*+}$

Numbers of cases are shown in parentheses. Significance *versus* reference group, $^{*}P < 0{\cdot}05$; $^{\dagger}P < 0{\cdot}001$. Significance *versus* calcific areas, $^{+}P < 0{\cdot}05$; $^{\S}P < 0{\cdot}02$

Results

The mean pancreatic tissue pressure observed in the four reference subjects was 10–20 mmHg, a figure in keeping with the findings of earlier investigations[7,8]. In all patients with chronic pancreatitis, mean pressure was elevated to 161–257 mmHg (*Table 1*). Although it was elevated at every site, values were generally greatest in the pancreatic head, and were correlated with the surgical assessment of severity and the presence of calcification.

Pancreatic tissue pressure was consistently higher in areas of calcific chronic pancreatitis than in non-calcified areas of diseased gland. The highest mean pressure recorded (662 mmHg) was in a patient with gross calcification of the pancreatic head (*Figure 1*). The lowest mean pressure in calcific disease (97 mmHg) was recorded from an area of the pancreas with minimal calcification. Compared with those in the reference group, elevation in pressure from regions of the gland with non-calcific chronic pancreatitis reached statistical significance in the body and tail, but not in the head of the pancreas. The highest mean pressure in non-calcific disease (374 mmHg) was measured in the pancreatic head of a young patient whose chronic pancreatitis followed a series of acute attacks.

Measurements of pancreatic ductal pressure were obtained in 10 patients, including seven with calcific disease. Only one of these patients showed gross dilatation of the pancreatic duct suitable for a drainage procedure. Unlike pancreatic tissue pressure, ductal pressure values were consistent throughout the gland. The mean pancreatic ductal pressure of 20 ± 4 mmHg (range 5–45 mmHg) lay towards the lower end of the range reported in previous studies of chronic pancreatitis[2–5]. There was no relationship between ductal and tissue pressures, the coefficient of correlation being 0·25.

There were no postoperative complications related to pancreatic needling.

Discussion

The data show a consistently high tissue pressure in severe chronic pancreatitis with and without radiological evidence of calcification. Although mean pancreatic tissue pressure was more than twice as high in calcific disease, there was considerable overlap with measurements in non-calcific areas of disease. Pressure varied between different regions of the same gland and between patients with similar severity of disease, as judged clinically and radiologically. In this preliminary study a threshold value above which pain is invariable has not been defined, but the high values recorded suggest that parenchymal hypertension contributes to the pain of chronic pancreatitis in the manner of a 'compartment syndrome'.

The evidence of increased pancreatic tissue pressure in chronic pancreatitis confirms Ebbehoj's experience, but the values obtained were considerably higher[7,8]. Unlike Ebbehoj's series, most patients in this study had neither duct ectasia nor pseudocysts but dense fibrosis and calcification, and the technique involved an infusion flow system rather than simple measurements of static pressure. The method used in this study reduces the risk of plugging of the cannula tip by solid components of pancreatic tissue, a recognized problem with pressure measurements in solid tissue[9]. Recordings measure tissue resistance to fluid infusion and may reflect parenchymal density rather than intracavity hydrostatic pressure.

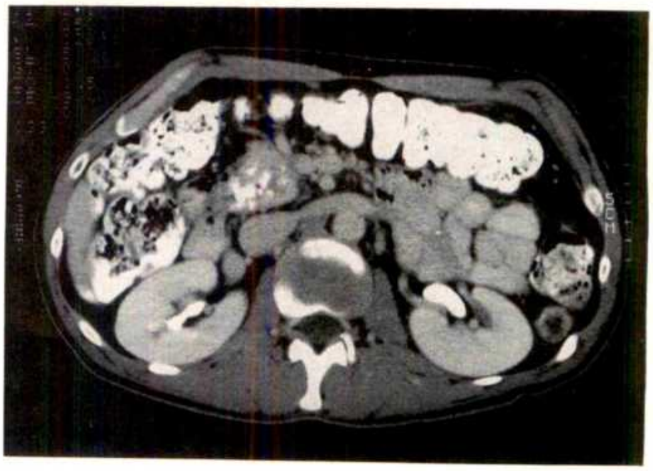

Figure 1 *Computed tomography scan showing calcification in the pancreatic head in a 51-year-old man with chronic alcoholic pancreatitis. There were very high tissue pressures in the calcified area with lower values in the body of the pancreas. The patient has had excellent pain relief following proximal pancreatectomy*

Unlike Ebbehoj *et al.* no direct relationship between ductal and tissue pressures in the pancreas was demonstrated, but this could be explained by the different category of patients and different methodology. Measurement of pancreatic tissue pressure has obvious advantages over measurement of ductal pressure: it is easier to record at operation, especially in the absence of ductal dilatation, and it is a more direct indicator of the pathological process in the pancreatic parenchyma. It has been suggested that a high pancreatic tissue pressure might facilitate influx of inflammatory mediators across the disintegrated perineurium of intrapancreatic nerve fibres and account for 'pancreatitis-associated neuritis'[10,11].

Our operative strategy for pain relief in patients with chronic pancreatitis involves pancreatectomy if the ductal system is not dilated. It is logical to remove the part of the gland most severely affected by disease. In patients with generalized pancreatitis but residual endocrine function, it can sometimes be difficult to decide whether to undertake proximal or distal resection[12]. In six such patients in the present series, pancreatic tissue pressures together with imaging data and operative examination of the pancreas were taken into consideration in reaching this decision. As experience increases, it may be that differential measurements within the gland will supplement the operative assessment of the pancreas in chronic pancreatitis.

References

1. Ihse I, Borch K, Larsson J. Chronic pancreatitis: results of operations for relief of pain. *World J Surg* 1990; **14**: 53–8.
2. Bradley EL. Pancreatic duct pressure in chronic pancreatitis. *Am J Surg* 1982; **144**: 313–16.
3. Madsen P, Winkler K. The intraductal pancreatic pressure in chronic obstructive pancreatitis. *Scand J Gastroenterol* 1982; **17**: 553–4.
4. Sato T, Miyashita E, Yamauchi H, Matsuno S. The role of surgical treatment for chronic pancreatitis. *Ann Surg* 1986; **203**: 266–71.
5. Okasaki K, Yamamoto U, Kagiyama S *et al.* Pressure of papillary sphincter zone and pancreatic main duct in patients with chronic pancreatitis in the early state. *Scand J Gastroenterol* 1988; **23**: 501–7.
6. Desa LA, Williamson RCN. On-table pancreatography: importance in planning operative strategy. *Br J Surg* 1990; **77**: 1145–50.

7. Ebbehoj N, Borly L, Madsen P, Svendsen LB. Pancreatic tissue pressure and pain in chronic pancreatitis. *Pancreas* 1986; **1**: 556–8.
8. Ebbehoj N, Borly L, Bulow J, Rasmussen SA, Madsen P. Evaluation of pancreatic tissue fluid pressure and pain in chronic pancreatitis: a longitudinal study. *Scand J Gastroenterol* 1990; **25**: 462–6.
9. Ebbehoj N, Svendsen LB, Madsen P. Pancreatic tissue pressure: techniques and pathophysiological aspects. *Scand J Gastroenterol* 1984; **19**: 1066–8.
10. Ihse I. Pancreatic pain. *Br J Surg* 1990; **77**: 121–2.
11. Beger HG, Buchler M, Bittner R. The duodenum preserving resection of the head of the pancreas (DPRHP) in patients with chronic pancreatitis and an inflammatory mass in the head – an alternative surgical technique to Whipple operation. *Acta Chir Scand* 1990; **156**: 309–15.
12. Williamson RCN, Cooper MJ. Resection in chronic pancreatitis. *Br J Surg* 1987; **87**: 807–12.

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Role of re-resection in early gastric stump carcinoma

Between 1971 and 1990, 26 patients were diagnosed as having an early carcinoma in the gastric remnant after ulcer surgery. Three patients with proximal tumour location were operated on with total gastrectomy. The surgical strategy in the remaining patients with tumour adjacent to the anastomosis was re-resection of at least 5–6 cm of the anastomotic area and restoration of gastrointestinal continuity with a Roux-en-Y loop. A margin of at least 2 cm from the carcinoma to the resection line was taken. There was no postoperative mortality. In three cases the preoperative endoscopic and histological judgement of tumour classification and stage was incorrect; when the surgical specimens were examined one patient was found to have advanced carcinoma and in the other two no malignancy could be found. Median follow-up was 15 years (range 3–19 years). During follow-up, six of the re-resected patients developed recurrences, all located in the gastric remnant. Four patients with recurrence underwent reoperation with total gastrectomy, one had exploratory laparotomy and one had no further surgery. No postoperative deaths occurred. Three of the six patients died from gastric carcinoma. We conclude that this surgical strategy failed to prevent local recurrence of an early form of gastric carcinoma, considered to be potentially curable in virtually all cases. Partial resection of the gastric remnant as the treatment of choice in patients with early gastric stump carcinoma cannot be recommended.

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Partial gastric resection has been a standard procedure for benign peptic ulcer disease during the past half century. This operation has, however, been proved to carry a twofold to fourfold increase in gastric cancer incidence in large cohort studies with adequate length of observation[1–4]. During the last two decades attention has been focused on early detection of gastric stump carcinoma and after the introduction of fibreoptic endoscopy a substantial proportion of the stump carcinomas found are in an early stage[5–9].

The outcome for patients with gastric carcinoma depends not only on early detection but also on the chosen treatment. Surgery is currently the only option for cure, but the prognosis for gastric cancer in the western hemisphere remains depressing[10–12]. If, however, the tumour can be found and treated aggressively at an early stage, survival is considerably improved, as shown in Japan[13].

Since 1973 we have been engaged in an endoscopic screening programme aimed at early detection and treatment of stump carcinoma[9]. The management of patients has followed a highly standardized programme, and the purpose of the present study was to analyse the results of a surgical approach using resection of the anastomotic area, i.e. re-resection in early gastric stump carcinoma.

Patients and methods

With the introduction of fibreoptic endoscopy in 1968 at the Department of Surgery, Lund University, Sweden, focus was placed on the increased risk of malignancy in the gastric remnant after ulcer surgery. A prospective screening programme was initiated in 1973 and ran until 1989 in a well defined cohort of patients operated on for peptic ulcer. The objective of the programme was to achieve a reduced mortality rate for gastric stump carcinoma[9]. Seventeen so-called early gastric carcinomas, i.e. carcinomas confined only to the mucosa and/or the submucosa, were found[14]. Two of the patients were treated surgically at another hospital and are therefore not included in this study. In addition to the patients with early gastric carcinoma detected in the screening programme, 11 other similar patients were diagnosed and treated at our department up to 1990. Apart from endoscopy with biopsy (and in many instances brush cytology) preoperative investigation in the beginning of the series included double contrast gastrography. However, this investigation did not add any valuable information and has not been routinely used since 1980.

In patients with a preoperative diagnosis of early gastric carcinoma situated in the anastomotic area, a resection including at least 5–6 cm of the distal gastric remnant was performed. The intention was to obtain at least a 2 cm free margin to the malignant lesion. The abdomen was in most cases entered through an upper midline incision. In some cases, however, a thoracoabdominal incision through the left pleural cavity was used. During the operation the gastric wall was palpated in search of additional tumours and in some cases the gastric remnant was opened for direct inspection of the mucosa. Splenectomy or resection of the pancreatic tail was not carried out. Only the lymph nodes in close proximity to the tumour area were excised *en bloc* with the gastric wall. The operative specimen was inspected by the surgeon and then sent for analysis of frozen sections from the proximal resection line during the operation. Gastrointestinal continuity was restored with a Roux-en-Y loop; a truncal vagotomy was added.

If the early gastric carcinoma was found to be separate from the anastomotic area, the patient was treated by total gastrectomy in the same manner as patients with resectable advanced gastric carcinoma.

Results

In all, 23 patients were judged before operation to have early gastric carcinoma in the anastomotic area and were treated with re-resection. There were no deaths after surgery. All but three patients were operated on before 1980 and the median time of follow-up was 15 years. The early gastric carcinoma was in all cases situated within the mucosa; the lymph nodes resected *en bloc* with the gastric specimen were all found to be free of tumour (*Table 1*). In three patients the preoperative tumour staging was incorrect. Two patients had a false positive diagnosis at the preoperative biopsy and in one the supposed

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early cancer had grown into the muscularis propria of the gastric wall. In spite of this the patient was considered 'cured' by the resection and additional surgery was not carried out. He was scheduled for annual endoscopic review but did not attend. Six years later he (case 6) developed a fatal carcinoma in the gastric remnant (*Table 2*).

Table 1 *Patients classified before operation as having early gastric carcinoma confined only to the anastomotic area*

Sex ratio (male:female)		22:1
Median age at ulcer surgery (years)		41 (25–57)
Surgical procedure at ulcer surgery	Billroth II gastrectomy	22
	Gastroenterostomy	1
Diagnosis at ulcer surgery	Gastric ulcer	7
	Duodenal ulcer	16
Median age at cancer diagnosis (years)		67 (45–78)
Median interval since ulcer surgery (years)		23 (10–45)
Clinical symptoms	Yes	12
	No	11
Endoscopic appearance according to Japanese classification of early gastric carcinoma[14] (two patients with two different types)	Type I	5
	Type IIa	4
	Type IIb	3
	Type IIc	2
	Type III	1
Not seen by endoscopist		10
Diagnosis from surgical specimen	Advanced gastric carcinoma	1
	Early gastric carcinoma	20
	Severe dysplasia	2
Dysplasia in resection line		3
Multifocal tumour growth		5
Laurén classification	Diffuse	6
	Intestinal	15
	Mixed type	0
	Not classified	2
Lymph node status	Tumour free	23
	Metastases	0
Median follow-up after re-resection (years)		15 (3–19)
Alive October 1990		7
Death from gastric cancer		3
Death from other malignant disease		5
Death from cardiovascular disease		8
Median age at death (years)		75·5 (59–90)

Values in parentheses are ranges

Five patients with early gastric carcinoma developed a recurrence or a new carcinoma in the gastric remnant (*Table 2*). In three of them (cases 1–3) dysplasia was found in the resection line at re-resection but the reappearance of cancer was in all three found outwith the anastomotic area (*Table 2*). In two of these patients the diagnosis was made 2 years after operation and in the third 8 years elapsed. All three were successfully treated with total gastrectomy. The remaining two patients died from gastric carcinoma and it was not possible to establish whether the recurrence originated from the anastomotic area or not. One man with a diffuse form of tumour according to the Laurén criteria[15] had a recurrence diagnosed after 17 months. A further laparotomy revealed a massive spread of the tumour. The other patient had an intestinal type of tumour[15]. He developed severe postgastrectomy problems after re-resection. To exclude a recurrence he was initially reviewed every third month with endoscopy. After 2 years he had yearly investigation. Seven years after the re-resection he was found to have a carcinoma occupying most of the gastric remnant. Computed tomography of the upper abdomen demonstrated a widespread tumour centred around the gastric remnant. The extension of the tumour in combination with severe heart disease prevented further surgery.

Three patients with tumour separated from the anastomotic area were primarily treated with total gastrectomy; none of them developed recurrence.

Discussion

Is a 29 per cent recurrence rate and a 14 per cent cancer mortality rate an acceptable result after re-resection for gastric stump carcinoma before operation staged as early gastric carcinoma? The surgical strategy was based on the state of the art during the early 1970s; the main reason for doing re-resection instead of total gastrectomy was that the reported operative mortality rate after the latter procedure, at that time, was about 30 per cent[16]. Furthermore, the concept of early gastric carcinoma was in its infancy, and it was unknown whether these often invisible lesions really would progress into an advanced cancer. Later reports also indicated that after diversion of the bile flow from the gastric mucosa, dysplasia was down-graded or disappeared[17]. A re-resection with a Roux-en-Y procedure would thus seem to have the ability to prevent further malignant development.

With present day knowledge we consider all recurrences and deaths potentially avoidable with a more aggressive surgical approach, but this could mean a shift in mortality from recurrence to postoperative mortality. Most reports with high postoperative mortality rates after total gastrectomy include a large proportion of patients operated on in the 1950s and 1960s. In recent years, however, it has been convincingly shown that the postoperative mortality rate after total gastrectomy irrespective of tumour stage can be kept at a level $\leqslant 5$ per cent[13,18–21], which is comparable to the postoperative

Table 2 *Patients with recurrence after re-resection*

Case	Sex	Age at re-resection (years)	Stage at re-resection	Growth pattern of tumour: Japanese classification	Growth pattern of tumour: Multifocal	Dysplasia in resection line	Time lag to recurrence (years)	Stage of recurrence	Laurén classification	Type of surgery at recurrence	Survival after recurrence (years)	Cause of death	Age at death (years)
1	Male	64	T_1N_0	IIa	No	Yes	2	T_1N_0	Intestinal	Total gastrectomy	12	Alive	
2	Male	67	T_1N_0	I	No	Yes	8	T_2N_0	Diffuse	Total gastrectomy	1	Endocarditis	76
3	Male	68	T_1N_0	I + IIc	Yes	Yes	2	T_2N_0	Intestinal	Total gastrectomy	5	Coronary infarction	75
4	Male	69	T_1N_0	IIb	No	No	1	T_4M_1	Diffuse	Exploratory laparotomy	< 1	Gastric cancer	70
5	Male	70	T_1N_0	IIa + b	Yes	No	7	T_4M_1?	Intestinal	Not operated	< 1	Gastric cancer	77
6	Male	67	T_2N_0	I	No	No	6	T_3N_2	Intestinal	Total gastrectomy	1	Gastric cancer	74

mortality rate after re-resection and Roux-en-Y diversion for non-malignant disease[22]. A higher operative mortality rate can hardly be considered acceptable nowadays after total gastrectomy. In a multicentre prospective randomized trial, Gouzi *et al.*[23] reported a postoperative mortality rate of 3·2 per cent after subtotal distal gastrectomy and of 1·3 per cent after total gastrectomy for cancers located in the distal part of the stomach. Pointer *et al.*[7] performed total gastrectomy in 15 patients with early stump carcinoma after Billroth II resection. There was no operative death or recurrence during a median follow-up of 4 years. Addressing the subject of postoperative morbidity, there is to date no definite proof that patients in the long run would fare worse after total gastrectomy regarding nutritional status or other postoperative sequelae, than after a high partial gastrectomy[24].

It was recently reported that patients with dysplasia in the gastric remnant have widespread gastric mucosal instability[25], and in an autopsy study Sons and Borchard found only 25 per cent of stump carcinoma to be situated in the anastomotic area[26]. This is, however, in contrast to other reports[27–29]. Five of the present patients had a multifocal tumour growth and in three this was first revealed at the histological examination of the surgical specimen. It is reasonable to believe that the reappearance of cancer after re-resection in some cases is the result of a missed multifocal lesion or the development of a new carcinoma. In three of the present patients the recurrence was found outside the anastomotic area. These findings support the opinion that the whole gastric remnant should be considered an area of malignant potential[30].

Only about half of the lesions could be detected at macroscopic inspection in this series. This makes it very difficult to determine the extent of a partial resection. In addition, it has been shown that dysplastic and malignant change has a patchy, often multifocal, distribution, and normal mucosa may be totally surrounded by mucosa with malignant change or *vice versa*[28,30,31]. This change also has a tendency to spread tangentially in a thin layer within the mucosa[31]. Therefore, evaluation of frozen sections during the operation is hazardous and of limited value.

Early gastric carcinoma is a lethal condition that eventually, although slowly, progresses into an advanced form[32]. New techniques are required to determine before operation whether a small gastric carcinoma breaches the muscularis propria. While this development is awaited, we agree with those who claim that the same surgical strategy should be used, irrespective of tumour stage, if the intention is cure[7,33]. The general principle in the treatment of gastric cancer situated distal to the cardiac region should be a transabdominal total gastrectomy with an R_2 lymph node dissection[13]. We have now adopted the same principle for early stump carcinoma, although there are no data in this study to support a wider lymph node dissection. This study has shown that a partial resection of the gastric remnant is insufficient for cure in many cases of early stump carcinoma. The conclusion is that patients with early gastric stump carcinoma should be subjected to total gastrectomy.

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References

1. Viste A, Opheim P, Thunold J *et al.* Risk of carcinoma following gastric operations for benign disease. *Lancet* 1986; **ii**: 502–5.
2. Caygill C, Hill M, Kirkham J, Northfield T. Mortality from gastric cancer following gastric surgery for peptic ulcer. *Lancet* 1986; **i**: 929–31.
3. Lundegårdh G, Adami H-O, Helmick C, Zack M, Meirik O. Stomach cancer after partial gastrectomy for benign ulcer disease. *N Engl J Med* 1988; **319**: 195–200.
4. Offerhaus G, Tersmette A, Huibregtse K *et al.* Mortality caused by stomach cancer after remote partial gastrectomy for benign conditions: 40 years of follow-up of an Amsterdam cohort of 2633 postgastrectomy patients. *Gut* 1988; **29**: 1588–90.
5. Osnes M, Løtveit T, Myren J, Serck-Hansen A. Early gastric carcinoma in patients with a Billroth II gastrectomy. *Endoscopy* 1977; **9**: 45–9.
6. Domellöf L, Janunger K-G. The risk for gastric carcinoma after partial gastrectomy. *Am J Surg* 1977; **134**: 581–4.
7. Pointer R, Schwab G, Königsrainer A, Bodner E, Schmid K. Early cancer of the gastric remnant. *Gut* 1988; **29**: 298–301.
8. Gandolfi L, Vaira D, Bertoni F *et al.* Cancer of the gastric stump in Italy, 1979–1986. *Gastrointest Endosc* 1988; **34**: 242–6.
9. Staël von Holstein C, Eriksson S, Huldt B, Hammar E. Endoscopic screening during 17 years for gastric stump carcinoma. A prospective clinical trial. *Scand J Gastroenterol* (in press).
10. Boddie A, McBride C, Balch C. Gastric cancer. *Am J Surg* 1989; **157**: 595–606.
11. Allum W, Powell D, McConkey C, Fielding J. Gastric cancer: a 25-year review. *Br J Surg* 1989; **76**: 535–40.
12. Lundegårdh G, Adami H-O, Malker B. Gastric cancer survival in Sweden. Lack of improvement in 19 years. *Ann Surg* 1986; **204**: 546–51.
13. Maruyama K, Okabayashi K, Kinoshita T. Progress in gastric cancer surgery in Japan and its limits of radicality. *World J Surg* 1987; **11**: 418–25.
14. Murakami T. Early gastric cancer. In: Murakami T, ed. *Gann Monograph on Cancer Research.* Vol II. Baltimore: University Park Press, 1971.
15. Laurén P. The two histological main types of gastric carcinoma: diffuse and so called intestinal type carcinoma. *Acta Pathol Microbiol Scand* 1965; **64**: 31–49.
16. Lundh G, Buru I, Kolig G, Richard C, Thomson J, van Elk P, Oszacki J. A co-operative international study of gastric cancer. *Ann R Coll Surg* 1974; **54**: 219–28.
17. Watt P, Sloan J, Spencer A, Kennedy T. Histology of the postoperative stomach before and after diversion of bile. *Br Med J* 1983; **287**: 1410–12.
18. Zilling T, Willén R, Walther B, Ranstam J. Prediction of survival in gastric carcinoma and a new histopathologic approach. *Anticancer Res* 1989; **9**: 487–500.
19. Schrock T, Way L. Total gastrectomy. *Am J Surg* 1978; **135**: 348–55.
20. Meyer H-J, Jaehne J, Pichlmayr R. Surgical treatment of gastric carcinoma: a retrospective analysis with special regard to the value of total gastrectomy as the operation of choice. *J R Coll Surg Edinb* 1989; **34**: 258–63.
21. Lindahl AK, Harbitz T, Liavåg I. The surgical treatment of gastric cancer: a retrospective study with special reference to total gastrectomy. *Eur J Surg Oncol* 1988; **14**: 55–62.
22. Ferguson H, MacLennan J, Taylor V, Torrance B. Outcome of revisional gastric surgery using a Roux-en-Y biliary diversion. *Br J Surg* 1990; **77**: 551–4.
23. Gouzi J, Huguier M, Fagniez P *et al.* Total *versus* subtotal gastrectomy for adenocarcinoma of the gastric antrum. *Ann Surg* 1989; **209**: 162–6.
24. Staël von Holstein C, Walther B, Ibrahimbegovic E, Åkesson B. Nutritional status after total and partial gastrectomy with a Roux-en-Y reconstruction. *Br J Surg* 1991; **78**: 1084–7.
25. Savalgi R, Corbishley C, Caygill C *et al.* Relation between severity and extent of precancerous lesions in the postoperative stomach. *Lancet* 1990; **336**: 413–16.
26. Sons H, Borchard F. Gastric carcinoma after surgical treatment for benign ulcer disease: some pathologic-anatomic aspects. *Int Surg* 1987; **72**: 222–6.
27. Morson B, Sobin L, Grundmann E, Johansen A, Nagayo T, Serck-Hansen A. Precancerous conditions and epithelial dysplasia in the stomach. *J Clin Pathol* 1980; **33**: 711–21.
28. Hammar E. The localization of precancerous changes and carcinoma after previous gastric operation for a benign condition. *Acta Pathol Microbiol Scand* 1976; **84**: 495–507.
29. Pointer R, Schwab G, Königsrainer A, Bodner E, Schmid K. Gastric stump cancer: ethiopathological and clinical aspects. *Endoscopy* 1989; **21**: 115–19.
30. Schrumpf E, Stadaas J, Myren J, Serck-Hanssen A, Aune S, Osnes M. Mucosal changes in the gastric stump 20–25 years after

partial gastrectomy. *Lancet* 1977; **ii**: 467–9.
31. Evans D, Craven J, Murphy F, Cleary B. Comparison of 'early gastric cancer' in Britain and Japan. *Gut* 1978; **19**: 1–9.
32. Tsukuma H, Mishima T, Oshima A. Prospective study of 'early' gastric cancer. *Int J Cancer* 1983; **31**: 421–6.
33. Carter K, Schaffer H, Ritchie W Jr. Early gastric cancer. *Ann Surg* 1984; **199**: 604–9.

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Announcement

The Golden Glove Award for The Royal College of Surgeons

The Golden Glove Award presented annually by the Worshipful Company of Glovers of London goes this year to the Royal College of Surgeons to recognize the extensive use of British-made rubber gloves in modern surgery. The Award was made by the Master, Mr Sidney Lea, to the Vice-President of the Royal College of Surgeons, Mr Adrian Marston, at a luncheon held at Stationers' Hall in the City of London on 23 July.

The Award is particularly apt this year, inasmuch as this is the 100th anniversary of the invention of latex gloves which revolutionized surgical practice. The first use of rubber gloves in surgery was by an American, William Stewart Halsted of Baltimore in 1891, who believed that if hospital nurses wore rubber gloves it would protect them against contact dermatitis. He also recognized that it must be easier to sterilize rubber gloves than human hands! By 1891/2 William Halsted had, in effect, invented aseptic surgery in place of the former antiseptic surgery – one of the greatest breakthroughs in medical hygiene.

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Proximal compared with distal adenocarcinoma of the stomach: differences and consequences

Interest in leading prognostic determinants of proximal gastric adenocarcinoma (PGA) in comparison with distally located adenocarcinoma (DLA) of the stomach led to an analysis of data from 506 patients with PGA and 484 patients with DLA operated on between 1 April 1982 and 31 October 1984 and participating in a multicentre observational study to validate tumour node metastasis (TNM) stage groupings. The proportion of men with PGA was slightly higher than that of men with DLA (69 versus *63 per cent). Men more often had cardia carcinomas than women (14* versus *9 per cent); 74 per cent of these men but only 43 per cent of the women were <65 years old. Evaluation of data by a log-linear model indicated a strong partial association (*P<*0·001) between age and site; patients younger than 65 years more often had PGA than older patients. Advanced tumour stage and the intestinal type of carcinoma were more frequently seen in the elderly. More than twice as many patients with PGA in comparison with those with DLA (35* versus *15 per cent) had palliative surgery (moderate association,* P<*0·05). This may have resulted from different stages at different sites; advanced carcinomas (TNM stages IIIb and IV) were more often diagnosed in patients with PGA than in those with DLA (60* versus *38 per cent). Residual tumour left after surgery was associated with deeper infiltration (*P<*0·001). No difference between PGA and DLA groups with respect to histological type of carcinoma was established, but residual tumour was more frequently associated with a diffuse type carcinoma (*P<*0·01). An overall tendency to poorer long-term prognosis in PGA was seen for all TNM stages, with and without residual tumour, except for TNM stage II with residual tumour, even though patients with PGA were younger than those with DLA. These differences in long-term prognosis, however, are based primarily on poorer short-term survival for PGA, particularly for TNM stages Ib and II without residual tumour. A significant risk of surgical management, particularly for early-stage tumours situated in the upper part of the stomach, has therefore been recognized. Surgeons should appreciate the higher surgical mortality rate for patients with PGA when curative treatment requires more risky surgical techniques.*

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The declining incidence of carcinoma of the stomach has apparently not affected carcinoma involving the upper stomach and oesophagogastric junction[1-6]. Whereas proximal gastric cancer has remained stable in absolute incidence it has increased in relative frequency[4]. The type of surgery for proximal cancer of the stomach remains a subject of controversy[1,7-10]. Difficulties in assessing the gastric and oesophageal extension of the tumour[1,8,10], in the importance of intraoperative staging for selecting appropriate surgery[11-13], in the choice of the optimal surgical procedure (total gastrectomy[9,12], proximal gastrectomy[9], oesophagogastrectomy[8]), in the type of incision (abdominal[14], transhiatal[8,15], right thoracotomy[16], left thoracotomy[1,7]), in the type and extent of lymphadenectomy[9,14,16], in the place of anastomosis (neck[8,17], thorax[1], abdomen[14]) and in the type of reconstruction of the digestive tract (gastric tube[10], jejunal segment[18], colonic segment[11]) characterize the problems of the operating surgeon. The purpose of this article is to compare the results of surgery for proximal gastric adenocarcinoma (PGA) with those for distally located adenocarcinoma (DLA) of the stomach. Data from a large prospective multicentre observational study of 1420 stomach cancer patients[13] were used to establish the leading prognostic determinants of PGA in comparison with DLA.

Patients and methods

Patients with PGA or DLA who were operated on between 1 April 1982 and 31 October 1984 in each of 22 departments of surgery participating in the Gastric Cancer TNM (tumour node metastasis) Study[13] were included in this analysis. PGA was defined as a lesion that extended to the oesophagogastric junction, whether its centre was located within the upper third of the stomach or not. Patients with DLA, defined as tumour located in the middle or lower third of the stomach and not infiltrating the margin between the upper and middle thirds of the stomach, were used for comparison. The staging of gastric cancer involved detailed assessment by the surgeon at laparotomy. The stomach was divided into thirds (upper, middle and lower) and the extent of involvement of the stomach wall was assessed (no serosa involvement or definite serosa involvement, i.e. invasion of contiguous structures according to the TNM system[19,20]). Lymph node involvement was categorized as N0-N2 according to the AJCC[19] and UICC[20] definitions and as N1-N16 as described in the Japanese General Rules[21]. The resected specimen was subjected to detailed

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pathological examination, which identified the depth of penetration of the stomach wall, whether the margins were free of tumour and the presence of secondary deposits in the various nodal groups and tiers, and the histological type of the primary according to Laurén (diffuse or intestinal)[22]. The tumour was finally staged by the TNM system and the operation categorized. Because the 1978 UICC classification[23] uses the terms 'radical resectable' and 'not radical resectable' without any definition of radicality, we decided that whenever the pathologists found microscopic residual tumour (R_1)[19] in a given patient, no radical resection had been performed[13]. When the surgeon's classification was R_2 (macroscopic residual tumour)[19] and the pathologist's classification was R_0 (no residual tumour)[19], we accepted the surgeon's statement because only he was able to identify residual tumour within the opened abdomen[13]. Whenever available, results of histopathological examination of specimens had priority over the surgeon's findings.

All data were prospectively recorded on special patient record forms and follow-up information was obtained every 3 months after surgery during the first year, every 6 months during the second year and then once a year, or until death[13]. The follow-up rate, 5 years after the end of the recruitment period, was 99·6 per cent[13]. After passing extensive error and plausibility checks using special computer programs, data were stored in the SIR database (Institute for Scientific Information, Deerfield, Illinois, USA).

Statistical methods

Because of the complex interactions between prognostic factors, it is not justifiable to look only at pairwise correlations. To investigate the higher-order interactions of the variables, depth of penetration (T_1 *versus* T_2–T_4[19,20]), age (≤ 65 *versus* >65 years), sex (male *versus* female), site (PGA *versus* DLA), histological type according to Laurén[22] (intestinal *versus* non-intestinal) and residual tumour (R_0 *versus* non-R_0)[19] were analysed by a log-linear model for multivariate tables. A hierarchical type of modelling up to third-order interactions was applied, the assessment of dependencies between factors being based on partial association (BMDP Statistical Software)[24]. Survival curves were computed by means of the Kaplan–Meier method[25], and the log rank test was used to quantify statistical differences.

Results

Out of 1420 previously untreated patients with histologically proven carcinoma of the stomach[13], 85 who also had a past history of a different kind of cancer were excluded, because a worse prognosis was assumed for these patients than for the rest of the sample. A further 292 patients with an undifferentiated type of adenocarcinoma were excluded because of its well known poorer prognosis in comparison with all other types of adenocarcinoma of the stomach, as were 42 patients without operation in whom the site of carcinoma could not be evaluated during surgery and in whom no specimen for histological examination of tumour type and resection lines was available. Finally, 11 patients were excluded because of missing information about the site of the primary, leaving 990 patients with adenocarcinoma of the stomach for further evaluation, 506 with PGA and 484 with DLA. The proportion of men with PGA was slightly higher than of men with DLA, and patients with PGA were younger than those with DLA (*Table 1*). The median (range) age of men with PGA was 63 (25–90) years and of men with DLA 67 (29–89) years. The analogous figures for women were 64 (31–87) and 68 (24–88) years respectively. Men had small tumours arising only from the cardia more often than women (site 151·0 according to UICC[19], 14·3 *versus* 8·8 per cent). About three-quarters of these men (74 per cent) were younger than 65 years in comparison with less than half (43 per cent) of the women.

A history of previous ulcer disease was found in one-third of patients with PGA and DLA. No significant difference between the two groups was found comparing their symptoms before surgery. Epigastric pain was more often found in patients with DLA than in those with PGA, and more patients with PGA than with DLA experienced weight loss or dysphagia. There was almost no difference between patients with PGA and DLA with respect to Karnofsky performance status, haemoglobin values or blood group (*Table 1*).

Table 1 *Personal and clinical data for patients with proximal gastric adenocarcinoma (PGA) and distally located gastric adenocarcinoma (DLA) of the stomach*

	Patients with PGA (*n* = 506)	Patients with DLA (*n* = 484)
Sex		
Men	348 (69)	303 (63)
Women	158 (31)	181 (37)
Age		
≤ 65 years	275 (54)	213 (44)
>65 years	231 (46)	271 (56)
Symptoms*		
Epigastric pain	328 (65)	350 (72)
Weight loss	300 (59)	217 (45)
No appetite	159 (31)	149 (31)
Vomiting	125 (25)	148 (31)
Dysphagia	114 (23)	11 (2)
Fatigue	103 (20)	104 (21)
Bleeding	70 (14)	64 (13)
Other symptoms	27 (5)	31 (6)
Karnofsky performance status†		
Normal activity	385 (76)	390 (81)
Incapable of work	96 (19)	75 (15)
Bedridden	23 (5)	14 (3)
Haemoglobin		
$<14/<12$ (men/women)	232 (46)	198 (41)
Blood group†		
O	188 (37)	169 (35)
A	235 (46)	241 (50)
B	49 (10)	38 (8)
AB	24 (5)	24 (5)

Values in parentheses are percentages. * More than one answer possible; † information missing for some patients

Table 2 *Type of gastrectomy and additional procedures in patients with proximal gastric adenocarcinoma (PGA) in comparison with distally located adenocarcinoma (DLA) of the stomach*

	Patients with PGA (*n* = 506)	Patients with DLA (*n* = 484)
Operation		
Total gastrectomy	268 (53)	110 (23)
Subtotal proximal gastrectomy	63 (12)	—
Subtotal distal gastrectomy	—	301 (62)
Palliation	175 (35)	73 (15)
Combined resection		
Splenectomy	237 (47)	69 (14)
Pancreas resection	54 (11)	11 (2)
Liver resection	9 (2)	4 (1)
Colon resection	10 (2)	4 (1)
Diaphragm resection	27 (5)	2 (–)
Oesophagus resection	119 (24)	—
Extended lymphadenectomy	124 (25)	88 (18)

Values in parentheses are percentages

Numbers and types of surgical procedures are shown in *Table 2*. Palliation, e.g. gastroenterostomy, was more than twice as common in patients with PGA. Combined resections, e.g. gastrectomy and splenectomy and resection of the tail of the pancreas, were needed almost three times as often for PGA than for DLA.

The 30-day mortality rate was slightly higher in patients with PGA than in those with DLA (*Table 3*). It was similar in both groups in patients of age ≤ 65 years, but higher in the older age group of patients with PGA. Men with PGA had a greater chance of dying than men with DLA, but no such difference was found in women. Death from gastrectomy in patients with PGA was higher than that in patients with DLA, and the mortality

Table 3 *Mortality rate of surgery in patients with proximal gastric adenocarcinoma (PGA) and distally located adenocarcinoma (DLA) of the stomach*

	Patients with PGA ($n=506$)		Patients with DLA ($n=484$)	
	Patients in the study	No. of deaths	Patients in the study	No. of deaths
Overall 30-day mortality rate	506	62 (12)	484	43 (9)
In relation to:				
Age				
≤65 years	275	20 (7)	213	12 (6)
>65 years	231	42 (18)	271	31 (11)
Sex				
Men	348	44 (13)	303	24 (8)
Women	158	18 (11)	181	19 (10)
Surgical procedure				
Total gastrectomy	268	28 (10)	110	8 (7)
Subtotal proximal gastrectomy	63	9 (14)	–	–
Subtotal distal gastrectomy	–	–	301	20 (7)
Palliation	175	25 (14)	73	15 (21)
Morbidity*				
Major surgical, e.g. leakage	97	36	80	15
Minor surgical, e.g. sinus	26	4	35	1
Cardiopulmonary problems	74	40	55	26
Other complications	46	15	40	6

Values in parentheses are percentages. * More than one answer possible

Table 4 *Proportion of R_0 and R_1/R_2 cases in relation to tumour node metastasis (TNM) stage (UICC 1987) for patients with proximal gastric adenocarcinoma (PGA) and distally located adenocarcinoma (DLA) of the stomach*

	Patients with PGA ($n=504$)*			Patients with DLA ($n=484$)		
TNM stage[20]	Total	R_0 cases	R_1/R_2 cases	Total	R_0 cases	R_1/R_2 cases
Ia	16	16 (100)	–	88	87 (99)	1 (1)
Ib	51	44 (86)	7 (14)	70	63 (90)	7 (10)
II	61	46 (75)	15 (25)	68	56 (82)	12 (18)
IIIa	73	37 (49)	36 (51)	72	49 (68)	23 (32)
IIIb	49	29 (59)	20 (41)	30	14 (47)	16 (53)
IV	254	39 (15)	215 (85)	156	24 (15)	132 (85)
Total	504	211 (42)	293 (58)	484	293 (61)	191 (39)

Values in parentheses are percentages. * Information on R status missing for two patients. According to the AJCC definition[19], R_0 = no residual tumour; R_1 = microscopic residual tumour; R_2 = macroscopic residual tumour

rate of proximal subtotal gastrectomy for PGA was as high as that for palliative surgery for PGA, and has therefore proved to be the most dangerous of all types of gastrectomy. Only the mortality rate for palliation in DLA was higher. Major complications like anastomotic leakage and cardiopulmonary problems leading to death were found much more frequently in patients with PGA than in those with DLA.

Early stages of gastric adenocarcinoma were rarely found in patients with PGA, but frequently found in those with DLA (*Table 4*). Of patients with PGA, 38 per cent had metastases, mainly peritoneal (20 per cent) or liver (12 per cent), while only 23 per cent of the patients with DLA had metastases (liver 9 per cent, peritoneal 9 per cent, other 5 per cent). Although the percentage of resections without residual tumour (R_0)[19] was high both in patients with PGA and in those with DLA, the percentage of patients with an advanced gastric adenocarcinoma, i.e. TNM stages IIIb and IV, having had resections with residual tumour either microscopically (R_1)[19] or macroscopically (R_2)[19] was much higher for PGA than for DLA.

Histological evaluation revealed an intestinal type[22] in 288 patients (57 per cent) with PGA and a non-intestinal type (which means diffuse or mixed type according to Laurén[22]) in 128 patients (25 per cent). The figures for DLA were 281 patients (58 per cent) and 167 patients (35 per cent) respectively, so little difference was found between PGA and DLA with respect to histological type. In 90 patients (18 per cent) with PGA and 36 patients (7 per cent) with DLA the Laurén type was unavailable. The 5-year survival rate was lower in patients with PGA than in those with DLA (*Table 5*). These differences were accentuated in patients with residual carcinoma (R_1 and R_2 cases) compared with patients without residual tumour (R_0 cases). So whenever residual tumour was left inside the abdomen (even in early gastric cancer stages such as stage Ib) survival was worse. To make sure that these differences in survival were not due to a much higher proportion of older patients with PGA than with DLA, age (≤65, >65 years) was evaluated according to TNM stage and site. In eight of 11 stage-group comparisons, patients with PGA were younger than those with DLA (*Table 6*).

The multivariate structure of the data as evaluated by a log-linear model is shown in *Figure 1*. Strong partial association ($P<0\cdot001$) was observed for age and site (more distal tumours for elderly patients), age and depth of penetration (older patients showed deeper penetration of the primary), age and Laurén histological type[22] (more intestinal tumours in elderly patients), depth of penetration and residual tumour (the deeper the penetration of the primary the more residual tumours were found), and depth of penetration and site (more advanced in patients with PGA). An intermediate partial association ($P<0\cdot01$) was found for the Laurén type and residual tumour (diffuse types were associated with more

Table 5 *Five-year survival in patients with no residual tumour (R_0 cases) and in those with residual tumour (R_1/R_2 cases) according to TNM stage groupings*[20]

	Patients with PGA ($n=504$)*			Patients with DLA ($n=484$)		
		5-year survival (%)			5-year-survival (%)	
TNM stage[20]	*n*	R_0 cases	R_1/R_2 cases	*n*	R_0 cases	R_1/R_2 cases
Ia	16	75	—	88	81	—
Ib	51	53(8)	14(13)	70	64(6)	57(19)
II	61	28(7)	32(12)	68	41(7)	17(11)
IIIa	73	31(8)	6(4)	72	33(7)	17(8)
IIIb	49	15(7)	5(5)	30	14(9)	6(6)
IV	254	5(3)	1(1)	156	12(7)	3(1)

Values are mean(s.e.m.). *Information on R status missing for two patients. According to the AJCC definition[19], R_0 = no residual tumour, R_1 = microscopic residual tumour; R_2 = macroscopic residual tumour

Table 6 *Results of the evaluation of age in R_0 and R_1/R_2 cases according to stage and site (PGA* versus *DLA), demonstrating a higher proportion of patients ≤65 years with PGA than with DLA*

	R_0 cases ($n=504$)				R_1/R_2 cases ($n=484$)			
	PGA patients ($n=211$)		DLA patients ($n=293$)		PGA patients ($n=293$)		DLA patients ($n=191$)	
TNM stage[20]	≤65 years	>65 years	≤65 years	>65 years	≤65 years	>65 years	≤65 years	>65 years
Ia	15	1	46	41	–	–	–	1
Ib	22	22	26	37	2	5	2	5
II	26	20	25	31	8	7	2	10
IIIa	22	15	27	22	25	11	11	12
IIIb	12	17	6	8	9	11	7	9
IV	17	22	12	12	117	98	49	83
Total	114	97	142	151	161	132	71	120

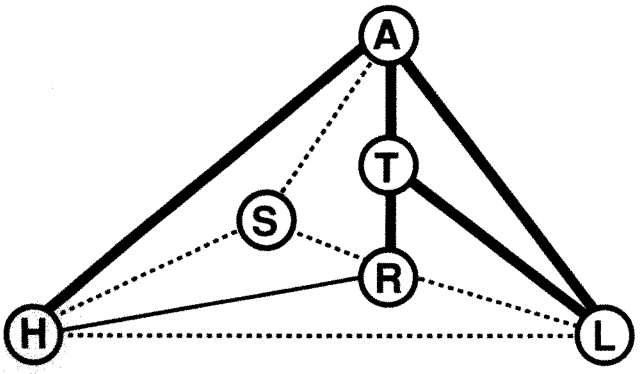

Figure 1 *Multivariate structure of the influencing factors: T, depth of penetration of primary tumour; A, age of patient; S, sex of patient; L, localization of primary tumour; H, Laurén classification; R, residual tumour. Using the measure of the partial association in the log-linear model:* ━━, $P<0{\cdot}001$; —, $P<0{\cdot}01$; -----, $P<0{\cdot}05$

residual tumours). Weak associations ($P<0{\cdot}05$) were found for residual tumours and site (more residual tumours were found in PGA), Laurén type[22] and site (more intestinal type tumours with PGA), sex and age (women were older), sex and Laurén type (women had more often a diffuse type according to Laurén[22]), and sex and residual tumour (women more often had residual carcinoma). There is also an indication that the relation of depth of penetration and residual tumours differs between proximal and distal localization, the only noticeable threefold interaction in the model, with a P value of 0·06. For proximal tumour sites, advanced carcinoma was more frequently associated with residual tumours compared with distal sites.

To evaluate short-term and long-term survival in those patients with PGA and DLA, survival curves were computed according to TNM tumour stage[19,20]. Since residual tumour is a significant factor for prognosis[13], calculations were made separately for subgroups of patients without (R_0 cases)[19] and with residual tumour (R_1 and R_2 cases)[19]. This permitted comparison of PGA and DLA of the same TNM stage with similar prognosis. *Figure 2* shows the survival curves for patients in TNM stages Ib–IV with DLA or PGA, comparing the R_0 cases (left side) with the R_1/R_2 cases (right side). There is an overall tendency for better long-term survival in patients with DLA, even though patients with PGA were younger (*Table 6*).

The short-term survival in the early TNM stages (Ib and II), with or without positive resection lines, was worse for PGA than for DLA, indicating that even early stages of tumour may carry a high surgical mortality rate when situated at the upper third of the stomach.

Discussion

This study of PGA and DLA in a large cohort of 990 patients with adenocarcinoma of the stomach with a short recruitment time (2·5 years) and a high 5-year follow-up rate (99·6 per cent) enables us to compare the same histological type of cancer according to different tumour stages in two different parts of the same organ. Treatment of carcinoma of the cardia has become an increasingly important part of the general and thoracic surgeon's practice[1,5,14,26]. Doing less than an *en bloc* resection in patients with potentially curable carcinoma of the

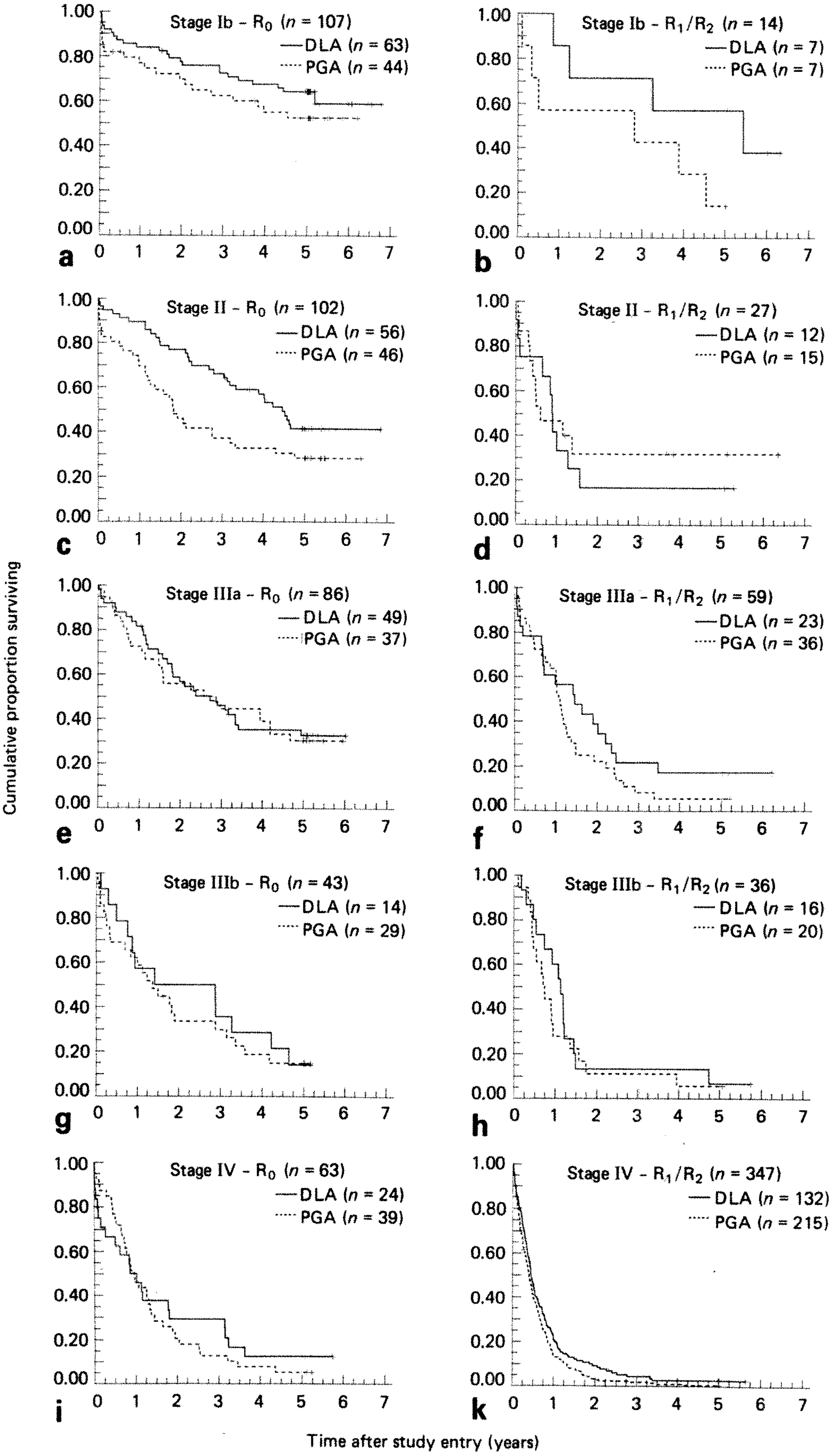

Figure 2 *Survival according to stage, site and residual tumour (left side without residual tumour, R_0; right side with residual tumour, R_1/R_2). R_0, no residual tumour; R_1, microscopic residual tumour; R_2, macroscopic residual tumour according to the Manual for Staging of Cancer of the American Joint Committee on Cancer AJCC*[19]*; PGA, proximal gastric adenocarcinoma; DLA, distally located adenocarcinoma. Censored observations are marked by +*

cardia is as wrong as doing an extensive operation for palliation in patients who are incurable[8,11]. However, to formulate a uniform policy for the ideal type of procedure is impossible[11,27] because preoperative computed tomographic diagnosis[28,29] and intraoperative frozen section are often falsely negative regarding the extent of the disease[1,10], endoscopy with biopsy can defect only superficial lesions[8,10], and operative assessment is of limited value because the microscopic extension of the growth cannot be observed[8].

Some may argue that PGA is a different disease from cancer elsewhere in the stomach[5,30]. Certainly, carcinoma of the cardia is characterized by older patients (mean age 61–65 years[10,14,15,17]; 46 per cent were >65 years in the present study), a high percentage of advanced tumour stages (between 50 and 74 per cent[7,10,12,14,15]; 75 per cent PGA stages IIIa, IIIb and IV in this study) and low resection rates (between 18 and 31 per cent[1,10,14]; 35 per cent in this study). Its site at the border between the thorax and abdomen can make the operation extremely difficult, dangerous and too often unsuitable for extended surgery. This results in high mortality rates (between 11 and 16 per cent[12,14,16,17]; 12 per cent in this study) and high morbidity rates (between 12 and 48 per cent[1,15,16]; 34 per cent in this study), with leakage of the oesophageal anastomosis as the main cause of death[1,7–10,12,16,17].

But which factors justify the belief that cardia carcinoma is a distinct entity[5,30]? Certainly we found more men with PGA than with DLA, and patients with PGA were younger than those with DLA. Also, a very impressive preponderance of younger men (<65 years of age), compared with women of the same age, occurred in the group with adenocarcinoma arising from the cardia. These findings indicate that younger men are much more at risk of developing a cardia carcinoma than younger women. Others have also found a male preponderance[5,7,10,14–17]; a relationship with cigarette smoking and/or the use of alcohol was strongly suspected[30,31].

It is interesting that the surgical mortality rate for 123 patients with carcinoma restricted to the small cardiac portion was almost as high as for 383 patients with PGA (14·6 *versus* 11·5 per cent). This suggests that it is not the extent of the primary at the upper part of the stomach but the difficulty in managing the lesion at this site at the border between the thorax and abdomen which is responsible for such a high mortality rate.

Leakage at the oesophageal–intestinal anastomosis is the most frequent and serious complication after gastrectomy for PGA[8–10,16,17]. The incidence was 10·6 per cent in the 11 university departments and 9·0 per cent in the 11 affiliated hospitals participating in this study and the associated mortality rates were 10·6 and 18·2 per cent respectively. These are high mortality rates, but they do not differ significantly from those reported by others[12,14,16,17]. That surgery causes these high mortality rates is impressively demonstrated by the survival curves of patients with early stages of PGA (*Figure 2a–d*). Compared with the survival curves for the same tumour stages of DLA, the patients with PGA show an initial dramatic drop, illustrating their high perioperative death rates. So a patient with an early-stage PGA may expect a much higher surgical risk than a patient with the same tumour stage located distally. This assumption is underlined when the 30-day mortality rates according to TNM stage are compared. Considering early and advanced tumour stages, the mortality rate in the present study remained on the same level for PGA (11·1 per cent in 203 patients with stage Ia–IIIa tumours and 9·7 per cent in 293 stages IIIb and IV) as in other studies[32], in contrast to the respective mortality rates for DLA. Here the mortality rate for early stage Ia–IIIa tumours was only 5·7 per cent in 298 patients, but 18·4 per cent for DLA of the advanced type (stages IIIb and IV) in 196 patients. The 30-day mortality rate was higher for the proximal lesion than for the distal lesion, but it was not clear whether this difference was maintained when operative mortality was excluded. We therefore evaluated the 5-year survival of all cases according to TNM stage and site (PGA *versus* DLA) with and without 30-day mortality rate, and found no indication of a reversal of the trend noted above..

It is interesting that, out of 18 patients with carcinoma restricted to the cardia who died, nine had negative and eight positive resection lines (one had missing information), indicating that positivity at resection lines may not increase mortality rates for patients with cardia carcinoma. We found similar figures in patients with PGA with and without residual tumour at resection lines (13·0 *versus* 11·4 per cent), whereas for DLA a pronounced difference was found (13·1 *versus* 6·1 per cent). This must be due to a large number of palliative gastrectomies for DLA in contrast to PGA, for which such extended surgery was thought to carry too high a risk.

Compared with DLA, PGA was associated with more advanced tumour stage in our patients and in others[7,10,12,14]. A strong partial association was noted between depth of penetration of the primary and site and more advanced tumour stage. This largely influences operability and resectability. Not surprisingly, palliative surgery was performed more than twice as often in patients with PGA as in those with DLA, which fits well with figures reported by others.

A partial association ($P=0{\cdot}0072$) between diffuse histological type according to Laurén[22] and residual tumour was found in this study. So the more advanced tumours with positive margins have been predominantly those of the diffuse type. However, a majority of diffuse type was not found in PGA compared with DLA, unlike the results of others[5]. Therefore the present results of histological examination of PGA and DLA do not indicate that PGA is associated with a certain histological type. In other words, there is no difference in disease type between PGA and DLA, but surgical intervention is more dangerous for PGA than for DLA, even in early-stage gastric carcinoma and even though patients with PGA are younger than those with DLA.

References

1. Ellis FH. Limited esophagogastrectomy for carcinoma of the cardia. *Ann Surg* 1988; **208**: 354–61.
2. Maruyama K, Okabayashi K, Kinoshita T. Progress in gastric cancer surgery in Japan and its limits of radicality. *World J Surg* 1987; **11**: 418–25.
3. Meyers WS, Damiano RJ, Postlethwait RW, Rotolo FS. Adenocarcinoma of the stomach: changing patterns over the last decades. *Ann Surg* 1987; **205**: 1–8.
4. Cady B, Ramsden DA, Stein A, Haggitt RC. Gastric cancer: contemporary aspects. *Am J Surg* 1977; **133**: 423–9.
5. Husemann B. Cardia carcinoma considered as a distinct clinical entity. *Br J Surg* 1989; **76**: 136–9.
6. Antonioli DA, Goldman M. Changes in location and type of gastric adenocarcinoma. *Cancer* 1982; **50**: 775–81.
7. Kawaura Y, Mori Y, Nakajima H, Takashi I. Total gastrectomy with left oblique abdominothoracic approach for gastric cancer involving the esophagus. *Arch Surg* 1988; **123**: 514–18.
8. Kirk RM. A trial of total gastrectomy, combined with total thoracic oesophagectomy without formal thoracotomy, for carcinoma at or near the cardia of the stomach. *Br J Surg* 1981; **68**: 577–9.
9. Kaibara N, Okitsugu N, Nishidoi H, Kimura O, Koga S. Proximal gastrectomy as the surgical procedure of choice for upper gastric carcinoma. *J Surg Oncol* 1987; **36**: 110–12.
10. Moreaux J, Msika S. Carcinoma of the gastric cardia: surgical management and long-term survival. *World J Surg* 1988; **12**: 229–35.
11. deMeester TR. Discussion. In: Ellis FH *et al.* Limited esophagogastrectomy for carcinoma of the cardia. *Ann Surg* 1988; **208**: 354–61.
12. Papachristou DN, Fortner JG. Selection of gastrectomy for adenocarcinoma arising in the gastric fundus. *J Surg Oncol* 1982; **21**: 165–9.
13. Rohde H, Gebbensleben B, Bauer P, Stützer H, Zieschang J. Has there been any improvement in the staging of gastric cancer? *Cancer* 1989; **64**: 2465–81.
14. deCalan L, Portier G, Ozoux JP, Rivallain B, Perrier M,

Brizon J. Carcinoma of the cardia and proximal third of the stomach. *Am J Surg* 1988; **155**: 481–5.
15. Goldfaden D, Orringer MB, Appelman HD, Kalish R. Adenocarcinoma of the distal esophagus and gastric cardia. *J Thorac Cardiovasc Surg* 1986; **91**: 242–7.
16. Griffith JL, Davis T. A twenty-year experience with surgical management of carcinoma of the esophagus and gastric cardia. *J Thorac Cardiovasc Surg* 1980; **79**: 447–52.
17. Welvaart K, Zwaveling A. Carcinoma of the oesophagus and gastric cardia. *Clin Oncol* 1980; **6**: 203–12.
18. Tanner NC. Neue Probleme der Magen-Chirurgie. *Langenbecks Arch Chir* 1951; **267**: 369–73.
19. AJCC. *Manual for Staging of Cancer*. 3rd ed. Philadelphia: J. B. Lippincott, 1987.
20. UICC. *TNM Classification of Malignant Tumors*. 4th ed. Berlin: Springer-Verlag, 1987.
21. Japanese Research Society for Gastric Cancer. The general rules for the gastric cancer study in surgery and pathology. *Jpn J Surg* 1981; **11**: 127–39.
22. Laurén P. The two histologic main types of gastric carcinoma: diffuse and so-called intestinal type carcinoma. *Acta Pathol Microbiol Scand* 1965; **64**: 31–49.
23. UICC. *TNM Classification of Malignant Tumors*. 3rd ed. Berlin: Springer-Verlag, 1978.
24. Dixon WJ (ed.). Program 4F. In: *BMDP Statistical Software*. Berkeley, California: University of California Press, 1985.
25. Kaplan EL, Meier P. Nonparametric estimates for incomplete observations. *J Am Stat Assoc* 1958; **53**: 456–81.
26. Kampschoer GHM, Nakajima T, van de Velde CJH. Changing patterns in gastric adenocarcinoma. *Br J Surg* 1989; **76**: 914–16.
27. Castrini G, Pappalardo G. Carcinoma of the cardia. *J Thorac Cardiovasc Surg* 1981; **82**: 190–3.
28. Moss AA, Schnyder P, Marks W, Margulis AR. Gastric adenocarcinoma: a comparison of the accuracy and economics of staging by computed tomography and surgery. *Gastroenterology* 1981; **80**: 45–50.
29. Triller J, Roder R, Stafford A, Schröder R. CT in advanced gastric carcinoma: is exploratory laparotomy avoidable? *Eur J Radiol* 1986; **6**: 181–6.
30. MacDonald WC. Clinical and pathologic features of adenocarcinoma of the gastric cardia. *Cancer* 1972; **29**: 724–32.
31. Flamant R, Lasserre O, Lazar R, Leguerinais J, Denoix P, Schwartz D. Differences in sex ratio according to cancer site and possible relationship with use of tobacco and alcohol. *J Natl Cancer Inst* 1964; **32**: 1309–46.
32. Hölscher AH, Schüler M, Thorban S, Bollschweiler E, Siewert JR. Das lokal fortgeschrittene Kardiakarzinom: lohnt die Resektion. *Dtsch Med Wochenschr* 1989; **114**: 1021–6.

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Devascularization following endoscopic sclerotherapy of oesophageal varices: dangers and difficulties

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Twenty-three patients underwent devascularization operations for acute variceal bleeding. All had received endoscopic sclerotherapy, either long-term or just before surgery. The oesophagus and peri-oesophageal tissues showed either oedematous or fibrotic reaction depending on the number and duration of sessions of sclerotherapy. These changes in the oesophagus and surrounding tissues were responsible for intraoperative oesophageal perforation and postoperative anastomotic leaks. To obviate these problems, stapling of the anterior and posterior walls of the stomach was tried and found to be safer than stapled transection of the oesophagus. During follow-up, varices reappeared in over 75 per cent of patients and were managed by further sclerotherapy. Patients who did not receive sclerotherapy had a higher incidence of rebleeding.

Endoscopic sclerotherapy is generally accepted as the primary treatment modality for the control of acutely bleeding oesophageal varices. Non-shunt devascularization operations are indicated if bleeding is not controlled by sclerotherapy and other conservative measures. These operations have been notorious in the past because of the high incidence of rebleeding. Devascularization after sclerotherapy has a comparatively high incidence of postoperative oesophageal suture line leakage which is an equally important factor contributing to the overall rates of mortality and morbidity. We report our experience of management of patients with acute variceal bleeding who have undergone devascularization following failure of sclerotherapy.

Patients and methods

Twenty-three patients underwent emergency devascularization procedures for uncontrolled variceal bleeding over a period of 2 years (October 1988 to October 1990). There were 20 men and three women, and their ages ranged from 14 to 65 years. Three patients had ascites and two were jaundiced. The cause of portal hypertension was non-cirrhotic portal fibrosis (NCPF) in nine, extrahepatic venous obstruction (EHO) in six and alcoholic cirrhosis in eight. Of the cirrhotic patients, two were Child's grade A and the remaining six were Child's grade B. All patients had received endoscopic sclerotherapy before surgery; seven had received long-term sclerotherapy, and 16 had acute variceal bleeding and received two to four courses of sclerotherapy 6–72 h before surgery. The sclerosant used in all patients was 100 per cent ethanol and the amount of sclerosant varied from 1 to 3 ml per variceal puncture site, injections being restricted to the lower 4–6 cm of the oesophagus. No vasoactive drugs were used but balloon tamponade was used in 11 patients for a period of 2–8 h. The transfusion requirements ranged from 4 to 20 units, mean(s.d.) 9(4) units.

Operative procedure

The operation was done transabdominally in a single stage. After splenectomy, the greater curve of stomach was devascularized, followed by devascularization of 6–8 cm of the lesser curve. The peri-oesophageal veins were carefully ligated and the oesophagus gently mobilized. An attempt was made to isolate and tape the vagus nerves. Oesophageal dissection was carried up to the diaphragmatic hiatus. In the initial 12 patients, the lower end of oesophagus was transected with an EEA stapler (US Auto Suture, Norwalk, Connecticut, USA). In the later 11 patients, stapling of the anterior and posterior gastric walls was done using a TA-55 stapler (US Auto Suture) through small holes made on both the greater and lesser curves about 2–3 cm below the oesophagogastric junction (*Figure 1*). The coronary vein was ligated just above the pancreas. Drains were placed near to the gastro-oesophageal junction.

Results

Operative difficulties

There was oesophageal and peri-oesophageal reaction of varying degrees in all patients. Patients who had had sclerotherapy in the immediate past had more of an oedematous reaction, and patients who had had chronic sclerotherapy had a reaction which was fibrotic in nature, making oesophageal mobilization difficult. Despite due care, oesophageal perforation occurred during surgery in two patients. The perforations were closed with a fundal patch. Both these patients had had chronic sclerotherapy. After operation the leak persisted and both patients died. Gallstones were found in a further patient and cholecystectomy was added to the procedure.

Postoperative mortality and morbidity

Out of 23 patients, six (26 per cent) died in hospital. The cause of death was oesophageal leak in four (EHO, two patients; NCPF, one patient; cirrhosis Child's grade B, one patient), liver failure in one (cirrhosis Child's grade B) and multisystem organ

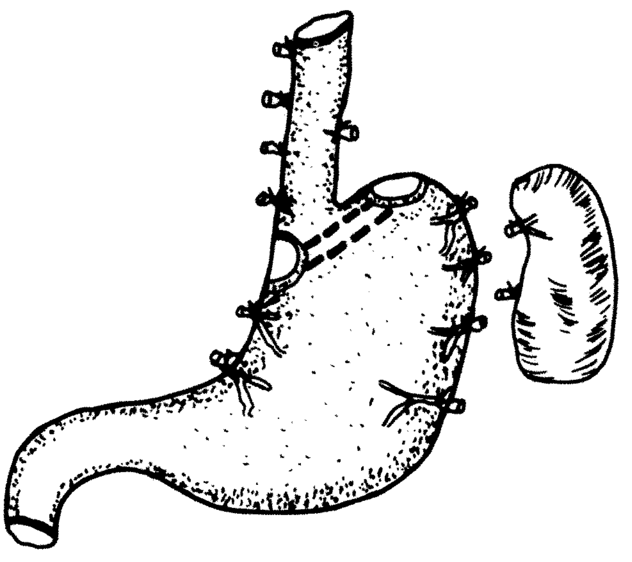

Figure 1 *Para-oesophagogastric devascularization and gastrofundic stapling. Broken lines indicate staple placement in anterior and posterior aspects of stomach*

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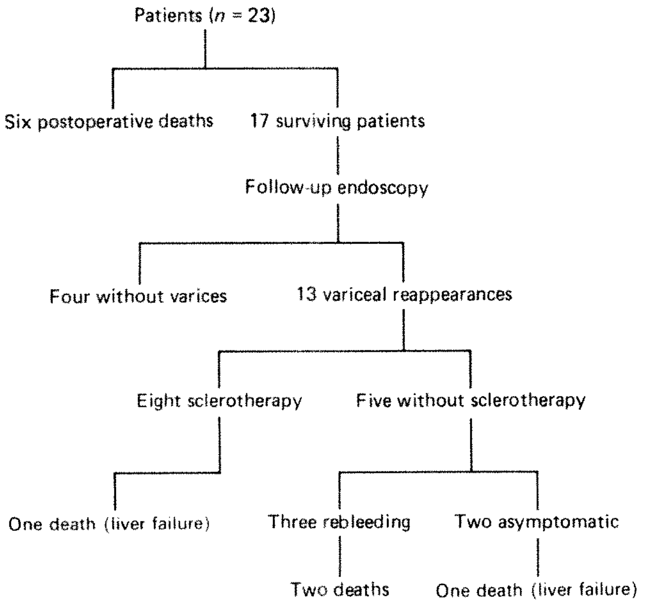

Figure 2 *Clinical course of patients after devascularization operations*

failure in one (NCPF). In total, five (22 per cent) patients developed an oesophageal leak in the postoperative period, including the two patients who had an oesophageal perforation during surgery. All these patients had stapler transection of the oesophagus. None of the patients in whom gastric stapling was performed developed a leak. All patients who had postoperative oesophageal suture line leakage were managed conservatively by nasogastric aspiration and jejunostomy feeding. Only one survived; the remaining four died from uncontrolled sepsis and malnutrition. Two (9 per cent) patients had rebleeding in the postoperative period; both settled with blood transfusions and other supportive measures.

Follow-up

The remaining 17 patients were followed up and repeat endoscopy was done at 3 months, 6 months and 1 year after surgery. In 13 (76 per cent) patients, varices reappeared within 6 months to 1 year. This reappearance of varices was independent of whether oesophageal or gastric stapling had been done. In four (24 per cent) patients, no varices were found 6–12 months after surgery. All patients who had varices were advised to undergo further sclerotherapy; eight had this done with no rebleeding and five patients refused (in three of whom bleeding recurred, and two died). The outcome for patients is shown in *Figure 2*. Overall, during follow-up, four (24 per cent) patients died, two with cirrhosis Child's grade B because of rebleeding and two from liver failure, one with cirrhosis Child's grade A and one with cirrhosis Child's grade B.

Discussion

In a patient with actively bleeding oesophageal varices, surgical intervention is usually called for once endoscopic sclerotherapy and other medical measures fail. As portal–systemic shunting carries high operative mortality and morbidity rates when undertaken on an emergency basis, especially in patients with poor liver function, most surgeons favour non-shunting devascularization procedures to control the bleeding in these desperate situations. The ideal devascularization procedure should arrest the haemorrhage immediately, with minimal mortality and morbidity rates, and should have a low incidence of rebleeding. A single operation which consistently meets these requirements has yet to be developed. It is generally agreed that for a devascularization procedure to be effective it should include both oesophagogastric devascularization and some sort of transection around the gastro-oesophageal junction.

Nowadays, patients presenting for devascularization operations have nearly always had sclerotherapy in an attempt to obliterate the oesophagogastric varices, either on a long-term basis or just a few hours or days before surgery. Emergency endoscopic sclerotherapy for active variceal bleeding, reported from this centre, has an overall success rate of 87 per cent in controlling bleeding[1]. In patients who are on long-term sclerotherapy, the aim is eradication of varices; rebleeding in this group was seen in only 2·9 per cent of patients[2]. The oesophageal and peri-oesophageal reaction to sclerotherapy is, in our experience (apart from the basic liver disease), also an important determinant of both intraoperative and postoperative mortality and morbidity rates. Patients who have had sclerotherapy just before surgery have mainly an oedematous reaction in the oesophageal wall and peri-oesophageal tissues. The mobilization of the oesophagus is not very difficult in these patients, but the chances of an anastomotic leak are high from a suture or staple line in an oedematous oesophagus. Of 16 patients who had sclerotherapy just before surgery, three developed an oesophageal leak. On the other hand, in patients who have had chronic sclerotherapy the lower end of the oesophagus is shrunken and fibrosed; the peri-oesophageal tissues are also fibrosed. Oesophageal mobilization in such cases is both risky and difficult. Both of our intraoperative oesophageal perforations occurred in this group of patients who had had long-term sclerotherapy. Although the perforations were closed with a fundal patch, the leak persisted after operation and both patients died. In the event of such a perforation occurring, it might be safer to perform a limited oesophagogastrectomy, as simple closures are probably bound to fail in the presence of unhealthy scarred tissue.

The high incidence of oesophageal problems in these patients is probably due to the use of 100 per cent ethanol as a sclerosant. This provokes a more severe oesophageal reaction than other conventional sclerosants. However, 100 per cent ethanol continues to be used as a sclerosant by local gastroenterologists as it is cheap, easily available and effective[3]. More attention needs to be paid to the amount of sclerosant injected and to early recognition of those patients who are not likely to respond to sclerotherapy, so that unnecessary sessions of injections are avoided.

The change of policy to stapling the stomach instead of the oesophagus was intended to avoid a staple line in the oedematous and fibrosed oesophagus. Stapling of the anterior and posterior gastric walls was described by Delaney[4], based on a concept proposed by Romero-Torres[5]. In addition to avoiding any oesophageal division or oesophagogastric resection, gastric stapling takes care of coexisting gastric varices, if any, which may be a cause of rebleeding in patients undergoing oesophageal transection. In the 11 patients in whom gastrofundic devascularization was carried out, no suture line leakage occurred and there was only one minor bleed. Four distinct advantages have been ascribed to the gastrofundic stapled devascularization[6]: no tension or stricture at the interruption site, simultaneous disconnection of gastric and oesophageal varices without transecting the fundus, preservation of distal oesophageal function, and the retention of serosa and good vascularity for healing.

In most patients undergoing non-shunting devascularization operations, varices reappear with time[7,8]. Variceal rebleeding was reported in 6·9 per cent of patients having this form of surgery in Japan[9]. Regular endoscopic follow-up of these patients has been recommended[10]. Reappearance of varices is believed to be related more to the extent of devascularization than to oesophagogastric transection[7]. Though the varices may not disappear after operation, or may reappear, there is a reduction in their diameter. It is believed that smaller diameter varices are less likely to bleed, and that should they bleed, blood loss will be less than in patients who do not have surgery[7]. Though the chances of rebleeding may be less, once bleeding occurs its management is not simple. We, like others[10], advocate endoscopic sclerotherapy for all recurrent or persistent varices after devascularization. Of the present patients, 76 per cent had recurrent varices and all of them were advised to have sclerotherapy. Of the five who refused, bleeding recurred in three and two died. Bleeding did not recur in the eight who received sclerotherapy, though one died from liver failure.

Patients in the present series had mild to moderate liver disease which is in contrast to other studies reported from the West, where most patients have cirrhosis with advanced liver disease. Comparisons with other reported series are difficult, not only because the aetiology of portal hypertension is different, but also because not all patients in these series have been operated on as emergency cases, a number of them having elective or prophylactic operations to prevent bleeding. In the review by Spence and Johnston[11], of 100 consecutive patients with varices who underwent stapled oesophageal transection, there were only 12 patients with an extrahepatic cause of hypertension. Of those patients with cirrhosis, 42 were Child's grade A and 24 were Child's grade B. None of the patients with extrahepatic disease died following surgery and at follow-up over 90 per cent remained free of bleeding. Of the 15 deaths in this series, only six occurred in the Child's A and B grades of patients. Koyama *et al.*[12] had 32 patients with non-cirrhotic portal hypertension; only two of these died following surgery. In our experience, the cause of death of the four patients without cirrhosis who died in the postoperative period was oesophageal leakage in three, while one patient died because of multisystem organ failure. No patient without cirrhosis died during follow-up.

In summary, it is our observation that in patients needing devascularization afer sclerotherapy, an important determinant of postoperative survival (apart from basic liver disease) is the presence or absence of an oesophageal leak, which, if present, is usually fatal. Gastrofundic stapling is not only as effective as stapled oesophageal transection for stopping variceal bleeding, but it is also safer, as the gastric staple line is unlikely to leak. Finally, recurrent varices after non-shunt operations should preferably be managed by prophylactic endoscopic sclerotherapy.

References

1. Sarin SK, Nanda R, Kumar N, Vij JC, Anand BS. Repeated endoscopic sclerotherapy for active variceal bleeding. *Ann Surg* 1985; **202**: 708–11.
2. Sarin SK, Sachdev G, Nanda R. Follow up of patients after variceal eradication. A comparison of patients with cirrhosis, noncirrhotic portal fibrosis and extrahepatic obstruction. *Ann Surg* 1986; **204**: 78–82.
3. Sarin SK, Sachdeva GK, Nanda R *et al.* Endoscopic sclerotherapy using absolute alcohol. *Gut* 1985; **26**: 120–4.
4. Delaney JP. A method for oesophago-gastric devascularization. *Surg Gynecol Obstet* 1980; **150**: 889–900.
5. Romero-Torres R. Hemostatic suture of stomach for the treatment of massive haemorrhage due to esophageal fibrosis. *Surg Gynecol Obstet* 1981; **153**: 710–12.
6. Cai Cheng-Ji, Wang Cheng-Pei. Use of staplers on oesophago-gastric varices. *Br J Surg* 1988; **75**: 1098–9.
7. Hosking SW, Johnson AG. What happens to esophageal varices after transection and devascularization. *Surgery* 1987; **101**: 531–4.
8. Koyangi N, Iso Y, Higashi H, Kitano S, Sugimachi K. Recurrence of varices after oesophageal transection: intra-operative and postoperative assessment by endoscopy. *Br J Surg* 1988; **75**: 9–11.
9. Inokuchi K. Present status of surgical treatment of oesophageal varices in Japan: a nationwide survey of 3588 patients. Japanese Research Society for Portal Hypertension. *World J Surg* 1985; **9**: 171–80.
10. Hashizume M, Kitano S, Yamaga H, Wada H, Sugimachi K. Eradication of oesophageal varices recurring after portal non-decompressive surgery by injection sclerotherapy. *Br J Surg* 1990; **77**: 940–3.
11. Spence RAJ, Johnston GW. Results in 100 consecutive patients with stapled oesophageal transection for varices. *Surg Gynecol Obstet* 1985; **160**: 323–9.
12. Koyama K, Tokagi Y, Ouchi K, Sato T. Results of oesophageal transection for oesophageal varices. Experience in 100 cases. *Am J Surg* 1980; **139**: 204–9.

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Oesophageal varices in a region of the Sudan endemic for *Schistosoma mansoni*

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In a field study of two villages in the Gezira, an area of the Sudan endemic for Schistosoma mansoni, *liver ultrasonography was used to detect subjects with Symmers' hepatic periportal fibrosis, some of whom underwent oesophagoscopy to detect oesophageal varices. The prevalence of oesophageal varices in subjects undergoing oesophagoscopy was 54 per cent and 67 per cent respectively, occurring mainly in males aged about 30 years. The varices were usually asymptomatic. Symptomatic varices (with a positive history of haematemesis) occurred in 4 per cent and 3 per cent respectively of subjects with sonographic evidence of liver periportal fibrosis. By detecting oesophageal varices in an asymptomatic phase, hepatic ultrasonography and fibreoptic oesophagoscopy may elucidate the natural history of the varices and their response to periodic anti-schistosomal chemotherapy.*

The mortality of *Schistoma mansoni* infection (*S. mansoni*) is mostly due to the development of Symmers' hepatic periportal fibrosis and subsequent portal hypertension with oesophageal varices[1,2]. The prevalence of oesophageal varices in patients with Symmers' fibrosis of the liver has been reported in symptomatic subjects in hospital and autopsy studies[2–4]. The magnitude of the problem in an area endemic for *Schistosoma* has not been adequately investigated.

Ultrasonographic examination of the liver is as accurate as wedge biopsy in detecting the presence of Symmers' fibrosis[5]. Characteristically the liver demonstrates dense echogenic bands around the portal vein and its branches[6].

This paper describes the prevalence of oesophageal varices in two villages in a region of the Sudan endemic for *Schistosoma* detected by oesophagoscopy in patients with sonographic evidence of Symmers' fibrosis.

Patients and methods

Abu Jin (population 1006) and El Nur (population 901), villages situated in the North Central and South Western parts of the Gezira scheme, were selected for study. These populations did not have chemotherapy for schistosomiasis before this study. A complete population census was carried out, and stools and urine samples were collected from all villagers for evidence of *Schistosoma* infection, as previously described[7].

A random sample of 418 villagers from Abu Jin and 242 from El Nur was selected for study using a randomization algorithm[8]. A medical history including haematemesis was obtained and clinical examination was performed. Abdominal ultrasonography using a portable ultrasound machine with 3·5 MHz transducer was carried out, and the presence of sonographic features of Symmers' fibrosis and its grade were determined as previously described[7]. Some of those with sonographic features of Symmers' fibrosis underwent fibreoptic gastroduodenoscopy. The light source and the suction machine were operated by a portable generator. The procedure was performed under local anesthesia of 2 per cent xylocaine spray to the oropharynx. The presence or absence of varices was confirmed by two endoscopists (A.M.A.S. and M.H.) using a connecting lecturescope and graded by the method of Conn and Brodoff[9]: grade 0, absent oesophageal varices; grade I, linear varices slightly elevating the mucous membrane; grade II, tortuous varices that did not encroach on more than half the diameter of oesophageal lumen; grade III, tortuous varices encroaching on more than half the diameter of the oesophageal lumen.

Statistical analysis was performed using the χ^2 and the Wilcoxon–Mann–Whitney test.

Results

In Abu Jin village the prevalence of *Schistosoma mansoni* infection was 45 per cent detected by stools positive for ova of *S. mansoni*. Of the 418 subjects randomly selected for investigation, 57 were found to have sonographic features of Symmers' fibrosis of the liver (a prevalence of 13·6 per cent), and of these, 46 subjects underwent oesophagoscopy (32 men and 14 women). Oesophageal varices were noted in 21 men and four women, a prevalence of oesophageal varices of 54 per cent among subjects with Symmers' fibrosis undergoing oesophagoscopy and of 6 per cent in the village population. In 14 subjects the varices were grade I, in nine grade II and in two grade III. The two subjects with grade III varices gave a history of haematemesis, with a prevalence of this morbidity of 4 per cent in subjects with Symmers' fibrosis and of 0·5 per cent in the village population.

In El Nur village the prevalence of *Schistosoma mansoni* infection was 56 per cent. Of the 242 subjects randomly selected for investigation, 38 showed ultrasonographic features of Symmers' fibrosis of the liver, a prevalence of 16 per cent. Of the 38 subjects with Symmers' fibrosis, 30 underwent oesophagoscopy (20 men and ten women). Oesophageal varices were found in 14 men and six women (a prevalence of 67 per cent in subjects with Symmers' fibrosis undergoing oesophagoscopy and 8 per cent in the village population). In 17 subjects the varices were grade I and in three grade II. Only one subject with grade II varices gave a history of haematemesis (a prevalence of 3 per cent in subjects with Symmers' fibrosis and of 0·4 per cent in the village population).

Oesophageal varices were found in men more commonly than women in both villages ($P < 0{\cdot}05$). The mean(s.d.) age of subjects with oesophageal varices was 34(15) years in Abu Jin village and 28(13) years in El Nur village. The peak age for disease was between 20 and 30 years. The spleen was palpable in only 16 of 45 of those patients with varices (36 per cent).

Table 1 shows that there was a significant relationship between the grade of Symmers' fibrosis and the grade of varices in the 76 subjects with Symmers' fibrosis from the two villages who underwent oesophagoscopy (Wilcoxon–Mann–Whitney test).

Discussion

Oesophageal varices in subjects suffering from *S. mansoni* infection are caused by Symmers' fibrosis of the liver[2]. The initial bleeding episode from the varices may be fatal but patients usually have multiple episodes over many years[10].

Most information regarding oesophageal varices in hepatic schistosomiasis has been derived from studies of hospital inpatients. In Kenya, 50 per cent of hospital patients with

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Table 1 *The relation between the grade of Symmers' fibrosis of the liver and of oesophageal varices in 76 subjects from Abu Jin and El Nour villages*

Grade of Symmers' fibrosis	Grade of varices 0	I	II	III	Total
1	22	23	3	0	48
2	9	6	7	0	22
3	0	2	2	2	6
Total	31	31	12	2	76

hepatic schistosomiasis had gastrointestinal bleeding[11]. In another series, 80 per cent of those with Symmers' fibrosis had oesophageal varices demonstrated by barium studies and/or oesophagoscopy[12]. We have previously reported that oesophageal varices secondary to bilharzial periportal fibrosis accounted for 42 per cent of patients presenting with haematemesis to Khartoum hospitals[3]. These figures do not necessarily reflect the state of affairs at village level in an area endemic for *Schistosoma* as has been shown by this study.

The accuracy of ultrasonography in detecting and grading Symmers' hepatic fibrosis has been reported elsewhere[5]. In this study the prevalence of oesophageal varices in villagers with ultrasonographic evidence of periportal fibrosis who underwent oesophagoscopy was found to be 54 per cent and 67 per cent, mainly in men between the ages of 20 and 30 years. The varices were mainly first and second grades and the majority occurred in the early grades of Symmers' fibrosis. These varices were usually asymptomatic. In a previous study we noted that the prevalence of Symmers' fibrosis was two to three times lower among a group of patients treated by periodic anti-schistosomal chemotherapy compared with an untreated population[13]. It would be of interest to study the effect of periodic anti-schistosomal chemotherapy on the prevalence of oesophageal varices in the village. Since the majority of varices were small and were detected in subjects with early periportal fibrosis, chemotherapy might allow the stabilization or amelioration of varices and reduce the risk of haematemasis.

The overall prevalence of bleeding oesophageal varices in the two village populations was 0·4 per cent and 0·5 per cent. This may represent the prevalence in other villages in the Gezira area or other endemic regions with similar prevalence of *S. mansoni* infection. Of the three million villagers of the Gezira scheme, therefore, there would be 12 000 to 15 000 with bleeding varices who may require therapy.

Splenomegaly was detected clinically in 36 per cent of those with oesophageal varices, indicating that the absence of splenomegaly does not preclude the presence of varices in subjects with ultrasonographic features of Symmers' fibrosis. Ultrasonography followed by oesophagoscopy accurately measures the morbidity of oesophageal varices secondary to hepatic schistosomiasis. These techniques may be used to study the natural history of oesophageal varices and their response to periodic anti-schistosomal chemotherapy in a prospective manner.

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References

1. Nash TE, Cheever AW, Ottensen EA, Cook JA. Schistosomiasis infections in humans: perspective and recent findings. NIH Conference. *Ann Intern Med* 1982; **97**: 740–54.
2. Cheever AW, Andrade ZA. Pathological lesions associated with *Schistosoma mansoni* infection in man. *Trans R Soc Trop Med Hyg* 1967; **61**: 626–39.
3. Saad AMA, Hassan MA. The pattern of haematemesis in Khartoum. *Sudan Med M J* 1986; **24**: 21–9.
4. El Masrie SH and Hassan MA. Splenecotomy and vasoligation for patients with haematamesis secondary to bilharzial hepatic fibrosis. *Br J Surg* 1982; **69**: 314–16.
5. Homeida MA, Abdel Gadir AF, Cheever AW *et al.* Diagnosis of pathologically confirmed Symmers' periportal fibrosis by ultrasonography: a prospective blinded study. *Am J Trop Med Hyg* 1988; **38**: 86–91.
6. Fataar S, Bassiony H, Satynath S, Vassileva J, Hanna RM. Characteristic sonographic features of schistosomal periportal fibrosis. *AJR* 1984; **143**: 69–71.
7. Homeida MA, Saad A, Dafalla A *et al.* Morbidity associated with *Schistosoma mansoni* infection as determined by ultrasound. A study in Gezira, Sudan. *Am J Trop Med Hyg* 1988; **39**: 196–201.
8. Friedman LM, Furberg CD, DeMets DL. *The Randomisation Process. Fundamentals of Clinical Trials.* Boston: Wright PSG, 1981: 48–50.
9. Conn HD, Brodoff M. Emergency oesophagoscopy in the diagnosis of upper gastrointestinal haemorrhage: a critical evaluation of its diagnostic accuracy. *Gastroenterology* 1964; **47**: 505–12.
10. Dunn MR, Kamel R. Hepatic schistosomiasis. *Hepatology* 1981; **1**: 653–61.
11. De Cock KM, Awadh S, Raja RS, Wankya BM, Lucas SB. Oesophageal varices in Nairobi Kenya: a study of 68 cases. *Am J Trop Med Hyg* 1982; **31**: 579–88.
12. Prata A. Schistosomiasis mansoni. *Clin Gastroenterol* 1978; **7**: 49–75.
13. Homeida MA, Dafalla AA, Kardaman MW *et al.* Effect of antischistosomal chemotherapy on prevalence of Symmers' periportal fibrosis in Sudanese villages. *Lancet* 1988; **ii**: 437–40.

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Self-dilatation of cervical oesophagogastric anastomotic stricture: a simple and effective technique

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Anastomotic stricture causing recurrent dysphagia is a serious problem occurring in patients after total oesophagectomy and cervical oesophagogastrostomy. We have developed a technique of self-dilatation of these strictures using a Foley catheter and have effectively managed ten patients. The technique is simple, painless, safe, cost-effective, and, as a domiciliary technique, patient acceptability is high.

Total oesophagectomy with cervical oesophagogastrostomy is a standard method of treatment for malignant and non-dilatable benign strictures of the oesophagus. However, an oesophageal anastomosis in the neck seems to be at higher risk of leakage than a reconstruction in the chest[1]. Predictably, a proportion of these leaks subsequently go on to cause stricture formation, obviating the benefits of this extensive surgical procedure. The consequent dysphagia is a difficult problem requiring frequent dilatation. We report a simple but successful technique for self-dilatation of such strictures.

Patients and methods

Patients who presented with dysphagia after cervical oesophagogastric anastomosis were evaluated by endoscopy. After confirming the diagnosis of anastomotic stricture and excluding an anastomotic recurrence by biopsy, patients underwent conventional dilatation of the oesophagogastric anastomosis using rigid dilators at the same sitting. Immediately afterwards, they were trained to carry out the procedure of self-dilatation described below.

The patient is asked to gargle with 4 per cent lignocaine hydrochloride solution for 5 min to produce oropharyngeal anaesthesia and reduce the gag reflex. He then swallows the lubricated end of a 14 Fr Foley catheter. When the catheter tip has passed beyond the stricture, the bulb of the catheter is inflated with 2–3 ml water. It is then pulled out with sustained traction (*Figure 1*). The volume of bulb inflation is increased stepwise by 1 ml each day until the balloon is just obstructed at the stricture site. After the technique is learnt, subsequent dilatations are practised at home as follows.

The procedure is carried out daily, in a fasting state, with increasing volumes of bulb inflation. The volume is increased stepwise until the patient has no residual dysphagia. This usually requires an inflation volume of 10 ml. The patient continues dilatation with this volume every day for a month and thereafter the procedure is carried out once each week for 3 months.

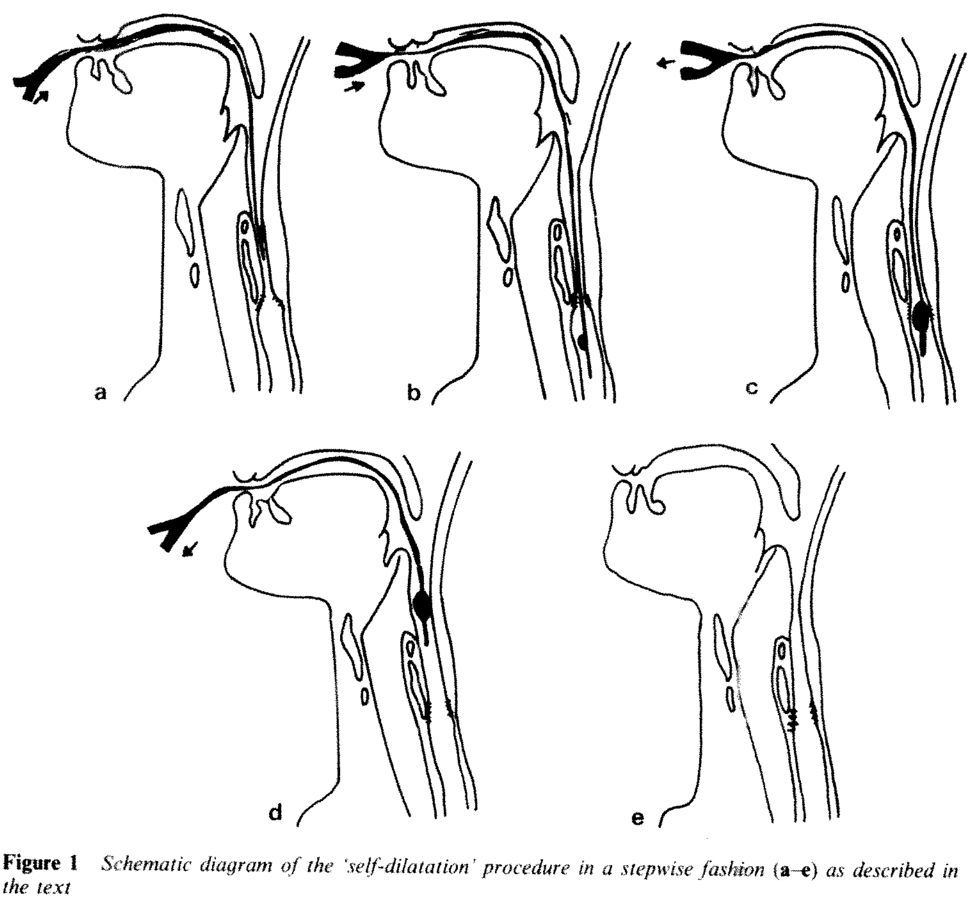

Figure 1 *Schematic diagram of the 'self-dilatation' procedure in a stepwise fashion* (**a–e**) *as described in the text*

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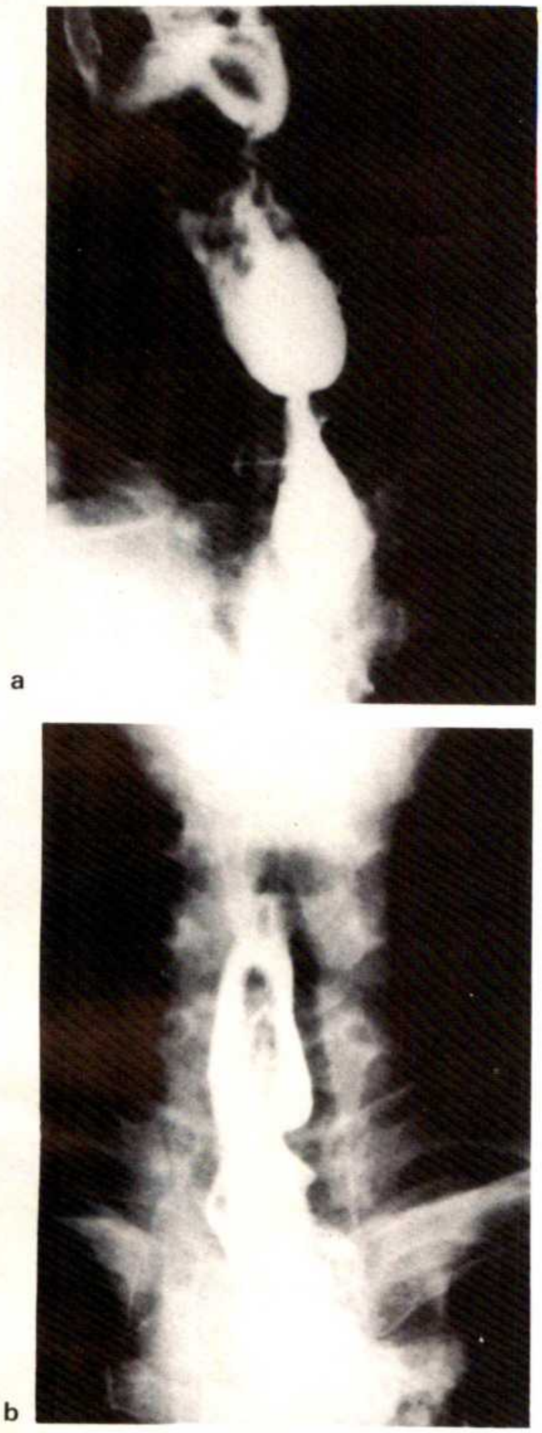

Figure 2 *Barium swallow radiograms showing* **a** *narrowing of oesophagogastric anastomosis and* **b** *the same patient after 3 months of self-dilatation showing adequately dilated anastomotic lumen*

Results

In eight of the ten patients normal swallowing was restored with this schedule. However, a further two patients required dilatation every 3 days (instead of every 7 days) for 3 months. They, too, thereafter maintained normal swallowing.

Discussion

Anastomotic stricture following oesophageal surgery is a difficult problem to manage. Various conventional methods using rigid dilators have been advocated in the past[2]. The technique described here is a simple and cost-effective method of treating a cervical oesophagogastric anastomotic stricture.

A significant problem occurs with the gag reflex, but this can be minimized by lignocaine gargles. The patient acceptability of the procedure is very high as the technique is painless. Swallowing is not painful after using this technique. The technique is domiciliary, obviating travel and loss of work. Furthermore, there is little risk of major complication such as massive tracheobronchial aspiration, perforation and mediastinitis which may occur after conventional dilatation[3].

Ten patients with cervical anastomotic strictures have been managed using this technique and normal swallowing was restored successfully in all. The technique is particularly suitable for such strictures as they involve a very short segment and are situated high up. Strictures occurring in anteriorly placed anastomoses (to antesternal or retrosternal visceral oesophageal substitutes) which are difficult to dilate by conventional rigid dilators[4] can also easily be dilated with this technique.

With this procedure dysphagia improves almost immediately after the first dilatation and by 3 weeks is almost totally relieved. However, to avoid recurrent dysphagia the procedure should be continued for 3 months. Eight patients remained free of dysphagia after dilatation performed in this manner, although a further two required dilatation every third day after the first month. All patients remained free of dysphagia after 3 months. There were no complications or failures using this technique and no patient developed recurrent dysphagia. The results were assessed not only by interrogation of the patients and observation of the act of swallowing, but also by barium swallow radiography (*Figure 2*).

Although cervical oesophagogastric anastomosis has a high leak rate with consequent stricture formation, such strictures can be managed easily using the technique described here. Though not attempted by us, the technique may also be helpful in managing thoracic anastomotic strictures, especially those situated high in the chest.

References

1. Duranceau A. Controversies in esophageal cancer surgery. *Can J Surg* 1989; **32**: 415–19.
2. Webb WA. Esophageal dilatation: personal experience with current instruments and techniques. *Am J Gastroenterol* 1988; **83**: 471–5.
3. Orringer MB. Complications of esophageal surgery and trauma. In: Greenfield LJ, ed. *Complications in Surgery and Trauma*. Philadelphia: J. B. Lippincott, 1984: 260–84.
4. Orringer MB. Transhiatal esophagectomy without thoracotomy for carcinoma of the thoracic esophagus. *Ann Surg* 1984; **200**: 282–8.

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1256–1258

Structural and functional smooth muscle injury after surgical preparation of reversed and non-reversed (*in situ*) saphenous vein bypass grafts

Intimal hyperplasia and isolated stenoses are major factors in determining the long-term patency of reversed and in situ *vein grafts. Surgical handling causes functional endothelial damage in reversed vein grafts but the effects of valvulotome use are unknown. Saphenous vein samples were taken after minimal dissection (control), distension with saline, or after the passage of a valvulotome. Rectangular strips of vein were mounted in an organ bath and cumulative noradrenaline (10^{-8}–10^{-5} M) dose contraction curves were performed. Compared with controls there was a significant reduction in the contractile response of both the distended and valvulotome-prepared veins ($P<0{\cdot}05$). Histological studies revealed partial endothelial cell loss in the distended group and total endothelial cell loss with patchy necrosis of the smooth muscle in the valvulotome group. These results suggest that the current use of a valvulotome not only renders the valves incompetent but also seriously damages the function of the smooth muscle layer.*

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The saphenous vein is the conduit of choice for infrainguinal bypass procedures[1] and, despite recent interest in the internal mammary artery[2], remains a popular conduit for coronary artery bypass grafting. Veins used for aortocoronary and above-knee femoropopliteal bypass are usually reversed so that the valves do not obstruct the flow of blood, but for femorodistal procedures to the popliteal artery below the knee and to calf vessels the *in situ* method is preferred[3,4]. In this technique the vein is not reversed, which permits a better size match between artery and vein graft at the distal anastomosis, and a valvulotome is passed along the vein to render the valves incompetent[5].

A major cause of failure of all vein grafts is the development of intimal hyperplasia in the graft which leads to narrowing of the lumen, a reduction in blood flow and subsequent thrombosis[6,7]. The aetiological processes involved in the development of intimal hyperplasia are poorly understood, but migration of smooth muscle cells from the media of the vein across the internal elastic lamina and into the intima where they proliferate and cause thickening appears to be a key event[8]. An additional cause of failure of vein grafts is the development of isolated graft stenoses, particularly during the first year after operation[6,9,10]. The aetiology of vein graft stenosis is also poorly understood and it is unclear whether or not this represents a similar pathological process to that of intimal hyperplasia.

It has been suggested that injury to the vein, caused by surgical preparation, might act as a stimulus to smooth muscle proliferation and migration[11]. Recent studies of reversed vein grafts have focused on damage caused to the endothelium associated with surgical handling of the saphenous vein. A considerable loss of the endothelial lining has been demonstrated[12] and the remaining endothelial cells are functionally impaired with reduced ability to release prostacyclin[13] and endothelium-derived relaxing factors[14]. However, less attention has been paid to the effects of surgical handling on smooth muscle cell histology and function. Because smooth muscle cell damage may be a factor in subsequent cellular migration and proliferation, we have studied the effect of surgical preparation on smooth muscle cell structure and function in saphenous veins prepared as reversed or *in situ* bypass grafts.

Patients and methods

Twenty-seven samples of saphenous vein were obtained from 22 patients undergoing either *in situ* femorodistal or reversed coronary artery bypass. The patients had a mean(s.e.m.) age of 68(2) years (range 49–89 years) and a mean(s.e.m.) blood pressure of 107(3) mmHg; none was hypertensive or diabetic. The samples of saphenous vein were handled surgically in three different ways. Samples in the first group (control) were obtained after minimal surgical dissection using a no-touch technique (seven patients, eight vessels); in the second group (distended) samples were taken after mobilization of the vein and uncontrolled distension with saline (eight patients, eight vessels); and samples in the third group (valvulotome) were obtained after full preparation for *in situ* grafting including the passage of a Hall valvulotome (seven patients, nine vessels). In each case a 2·5-mm valvulotome was used and passed as atraumatically as possible. All samples of vein were taken from the calf region, which represented the distal end of the vein graft for the *in situ* group. The veins were transported from the operating theatre to the laboratory in cold (4°C) calcium-free physiological salt solution.

A ring of vein, 5 mm in length, was cut open to form a rectangular strip. One end of the vein was attached to a stainless steel plate and the other to a force transducer to measure isometric contraction. The stainless steel plate and vein were placed in an organ bath containing physiological salt solution (composition: NaCl 118 mM; $NaHCO_3$ 25 mM; KCl 4·5 mM; KH_2PO_4 1 mM; $CaCl_2$ 2·5 mM; $MgSO_4 \cdot 7H_2O$ 1 mM; glucose 6 mM) at 37°C and gassed with a 5 per cent CO_2/95 per cent O_2 mixture to achieve a pH of 7·45[15] (*Figure 1*).

After an equilibrium period of 1 h, each vein was stretched and the passive tension was set to achieve a maximum contractile response to noradrenaline. A further equilibrium period of 1 h was allowed to elapse before a cumulative dose contraction curve to noradrenaline (10^{-8}–10^{-5} M) was performed in the presence of 10 μM cocaine. Finally, the vessels were fixed with 2 per cent glutaraldehyde in buffer solution and representative sections were processed for histological assessment. Paraffin sections (4 μm) were stained with either haematoxylin and eosin or elastin van Gieson, and the degree of endothelial and smooth muscle cell damage assessed.

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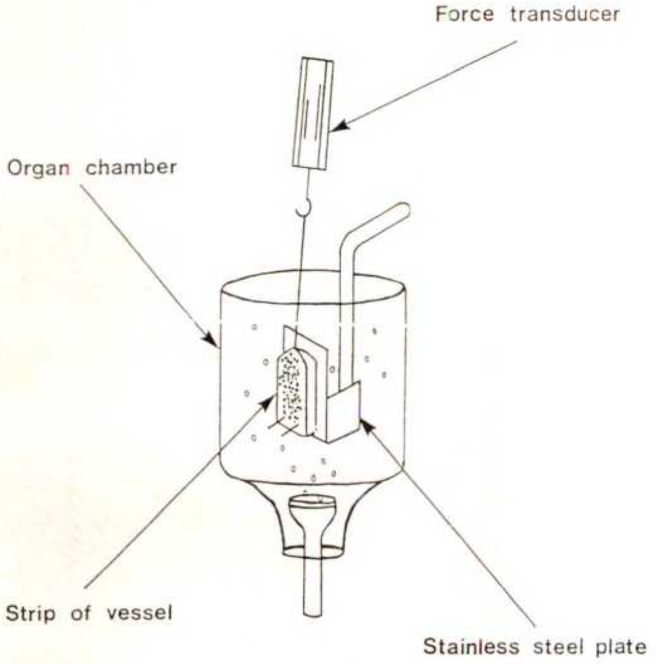

Figure 1 *Diagrammatic illustration of a vein mounted on a plate and suspended in a heated, gassed organ bath*

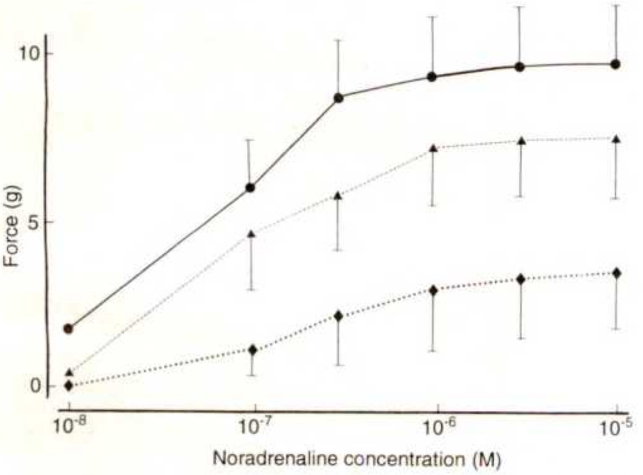

Figure 2 *Contractile response of human saphenous veins to noradrenaline in control (●), distended (▲) and valvulotome (◆) groups. Values are mean(s.e.m.)*

The contractile responses are reported as mean(s.e.m.) values. Significant differences were determined by using two-way analysis of variance with a Scheffé test, taking $P<0{\cdot}05$ as significant.

Results

Contraction studies

The resting tension needed to elicit a maximum contraction to noradrenaline was similar for the control, 2·43(0·30)*g*, distended, 2·63(0·26)*g*, and valvulotome, 1·50(0·55)*g*, groups. The saline-distended and valvulotome-prepared veins showed significantly reduced contractile responses to noradrenaline when compared with controls ($P<0{\cdot}05$) (*Figure 2*). The control veins achieved a maximum contraction of 9·56(1·85)*g*, with a 20 per cent decrease of the response to 7·61(2·56)*g* after saline distension and a 64 per cent reduction to 3·42(1·71)*g* after passage of a valvulotome. In addition, the concentration of noradrenaline required to induce a half-maximal contraction (ED_{50}) was slightly increased in the distended group, 0·17(0·05) μM, and was higher in the valvulotome group, 0·40(0·23) μM, compared with the controls, 0·06(0·02) μM.

Histological assessment

The intima of each vein was normal on naked-eye examination. Histological assessment of the control group (seven veins) showed that the medial smooth muscle was preserved in each specimen. In six of the seven control veins examined, the endothelium was intact (*Figure 3*), but patchy endothelial cell loss was seen in one vein.

In the eight veins which had been distended with saline, six showed patchy endothelial cell loss with a minor degree of smooth muscle cell damage and the remaining two showed severe endothelial cell loss with some smooth muscle cell necrosis.

After passage of the valvulotome (seven veins) all veins showed total loss of endothelial cells with a variable degree of smooth muscle cell necrosis .

Discussion

The development of intimal hyperplasia and graft stenoses may be a major barrier to long-term patency of reversed and *in situ* saphenous vein grafts[6,11,16]. The factors that stimulate these processes are unknown, but proliferation of smooth muscle cells that have migrated into the intima appears to be a key event which leads to thickening of the intimal layer[8]. It has been suggested that surgical damage during preparation of the saphenous vein for bypass grafting might be a causative factor in the development of intimal hyperplasia. Histological studies of reversed saphenous vein grafts have shown that surgical handling which includes mobilization, ligation of side-branches and distension with saline to identify leaks, causes significant damage to the endothelium. More recently, functional studies in reversed vein grafts have demonstrated reduced production of prostacyclin[13], a powerful inhibitor of platelet aggregation, and of endothelium-derived relaxing factor[14].

By contrast, few studies have been concerned with the effects of surgical handling on the contractile function of the saphenous vein. In particular, the effects of passing a valvulotome, an essential part of preparation of *in situ* grafts, are unknown. The

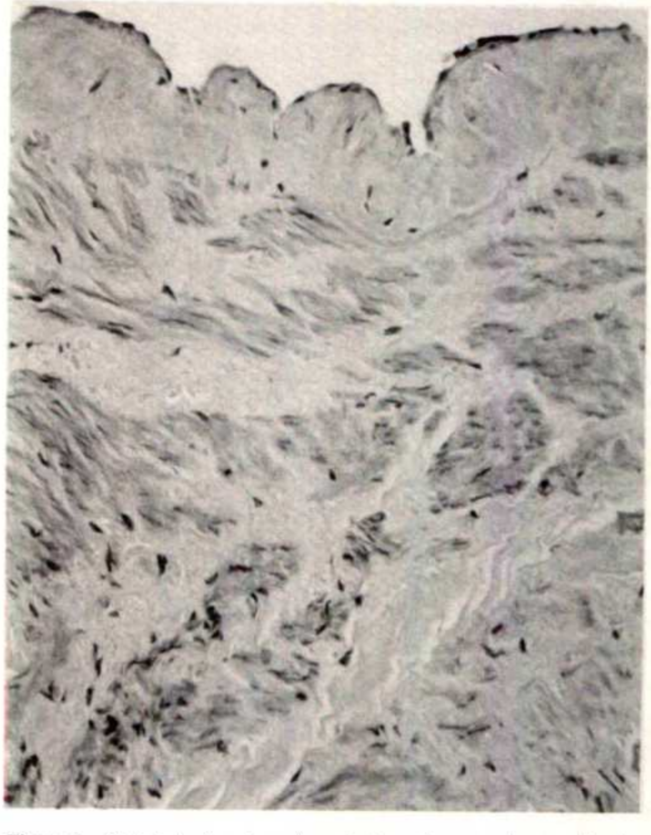

Figure 3 *Histological section of a vein from the control group showing preservation of endothelial cells and medial smooth muscle (× 230)*

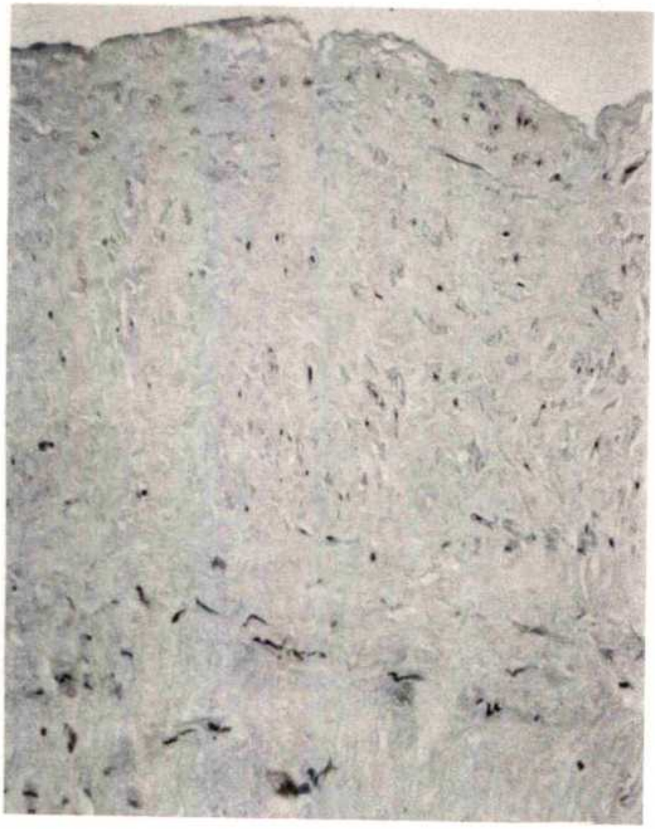

Figure 4 *Histological section of a vein from the valvulotome group showing endothelial cell loss and patchy necrosis of medial smooth muscle* (× *230*)

present results show that surgical preparation of reversed and *in situ* vein grafts leads to functional damage of the smooth muscle layer. Passage of a valvulotome and distension with saline both reduced the maximum contractile response to noradrenaline compared with the control group. The functional impairment was greatest for the valvulotome group, many of these veins being unable to maintain a sustained contraction on a second exposure to noradrenaline, whereas multiple reproducible curves were obtained with the control and distended vein groups. Histological examination of the veins in the valvulotome group showed smooth muscle cell damage with necrosis, whereas the control and distended groups had well preserved smooth muscle architecture. However, histological assessment may underestimate the degree of smooth muscle damage in the distended group, because although these veins appeared structurally intact they also had some reduction in contractile response.

Although this study illustrates well the traumatic effects of valvulotome use, it is interesting to note that uncontrolled distension with saline also produces functional smooth muscle damage. If smooth muscle injury is a contributory factor to the development of intimal hyperplasia, the present study supports its occurrence in both reversed and *in situ* vein grafts. Further studies of the role of smooth muscle cells in this process are warranted, especially to determine whether functional damage to these cells is an event that initiates migration and proliferation. While awaiting results from such studies, it would seem prudent for surgeons to handle the vein with great care and, in the case of the *in situ* graft technique, to use the smallest valvulotome available, passing it as atraumatically as possible.

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References

1. Bergan JJ, Yao JST, Flinn WR, Graham LM. Prosthetic grafts for the treatment of lower limb ischaemia: present status. *Br J Surg* 1982; **69**(Suppl): 34–7.
2. Sims FH. The internal mammary artery as a bypass graft? *Ann Thorac Surg* 1987; **44**: 2–3.
3. Hall KV. The great saphenous vein used *in-situ* as an arterial shunt after extirpation of vein valves. *Surgery* 1962; **51**: 492–5.
4. Leather RP, Powers SR, Karmody AM. A reappraisal of the *in situ* saphenous vein bypass: its use in limb salvage. *Surgery* 1979; **85**: 453–61.
5. Skageth G, Hall KV. *In situ* bypass experience with a new vein stripper. *Surgery* 1972; **6**: 1–6.
6. Szilagyi DE, Elliott JP, Hageman JH, Smith RF, Dall'Olmo CA. Biological fate of autogenous vein implants as arterial substitutes. *Ann Surg* 1973; **78**: 232–46.
7. Fuchs JCA, Mitchener JS, Per-Otto H. Postoperative changes in autologous vein grafts. *Ann Surg* 1978; **188**: 1–15.
8. Dilley RJ, McGeachie JK, Prendergast FJ. A review of the histological changes in vein-to-artery grafts, with particular reference to intimal hyperplasia. *Arch Surg* 1988; **123**: 691–6.
9. Moody P, de Cossart LM, Douglas HM, Harris PL. Asymptomatic strictures in femoropopliteal vein grafts. *Eur J Vasc Surg* 1989; **3**: 389–92.
10. Grigg MJ, Nicolaides AN, Wolfe JHN. Detection and grading of femorodistal vein graft stenoses: Duplex velocity measurements compared with angiography. *J Vasc Surg* 1988; **8**: 661–6.
11. Campbell PA, McGeachie JK, Prendergast FJ. Vein grafts for arterial repair: their success and reasons for failure. *Ann R Coll Surg Engl* 1981; **63**: 257–60.
12. Ramos JR, Berger K, Mansfield PB, Sauvage LR. Histological fate and endothelial changes of distended and nondistended vein grafts. *Ann Surg* 1976; **183**: 205–28.
13. Angelini GD, Breckenridge IM, Psaila JV, Williams HM, Henderson AH, Newby AC. Preparation of human saphenous vein for coronary artery bypass grafting impairs its capacity to produce prostacyclin. *Cardiovasc Res* 1987; **21**: 28–33.
14. Angelini GD, Christie MI, Bryan AJ, Lewis MJ. Surgical preparation impairs release of endothelium derived relaxing factor from human saphenous vein. *Ann Thorac Surg* 1989; **48**: 417–20.
15. Rubany GM, Vanhoutte PM. Hypoxia releases a vasoconstrictor substance from the canine vascular endothelium. *J Physiol* 1985; **364**: 45–56.
16. Wolfe JHN, McPherson GAD. The failing femorodistal graft. *Eur J Vasc Surg* 1987; **1**: 295–6.

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Prevalence of abdominal aortic aneurysm in patients with occlusive peripheral vascular disease

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Over a 1-year period, 242 patients with peripheral vascular disease underwent abdominal ultrasonography to detect the presence of an abdominal aortic aneurysm. In 34 (14 per cent) an abdominal aortic aneurysm was found; half of these aneurysms were >4 cm in diameter. In addition, 16 patients had ectatic aortas. Abdominal aortic aneurysms were more common in men than in women (17 versus *8 per cent). Patients with claudication were as likely to have an abdominal aortic aneurysm as those with rest pain or gangrene. The presence of aortoiliac occlusive disease increased the chance of an aneurysm being present* ($P<0{\cdot}02$)*. Patients with occlusive peripheral vascular disease are a high-risk group with regard to the development of an abdominal aortic aneurysm. Patients with proximal occlusive disease represent a subgroup at even higher risk.*

Increasing numbers of abdominal aortic aneurysms are being diagnosed and treated[1]. Approximately 5 per cent of asymptomatic men between the ages of 65 and 74 years have been shown by abdominal ultrasonography to have an abdominal aortic aneurysm[2]; half of these aneurysms are >4 cm in diameter. An increased risk has been found in patients with hypertension[3], coronary artery disease[4], peripheral vascular disease[5], other aneurysms[6] or a positive family history[7]. The aim of this study was to look in more detail at the prevalence of abdominal aortic aneurysm in patients with occlusive vascular disease, and to correlate the presence of abdominal aortic aneurysm with clinical findings.

Patients and methods

Between September 1989 and September 1990 all patients presenting with symptoms of chronic, or acute-on-chronic, occlusive peripheral vascular disease were examined for the presence of an abdominal aortic aneurysm and underwent abdominal ultrasonography using a Diasonics DRF 100 real time scanner (Diasonics Sonotron Ltd., Bedford, UK) with a 3·5 MHz probe. The maximum and minimum infrarenal aortic diameters were noted. An aneurysm was defined as a localized aortic dilatation. It was diagnosed if the maximum diameter of the infrarenal aorta was either >3·5 cm or >1·5 times that of the aorta at the level of the renal arteries. The aorta was defined[5] as ectatic if it was diffusely and irregularly dilated with a minimum diameter of 3 cm.

All patients had Doppler arterial pressure measurements and calculation of ankle:brachial pressure indices. In addition, since one of the aims of the study was to correlate the presence of an aneurysm with the site of occlusive disease, an intravenous digital subtraction angiogram was performed in each case.

Results

Two hundred and forty-seven patients presented; three declined investigation and the aorta was not visualized by ultrasonography in two, leaving 242 patients for analysis.

An abdominal aortic aneurysm was found in 34 patients (14 per cent). The clinical details of the patients are shown in *Table 1*. All aneurysms >5 cm in diameter and seven of the ten aneurysms between 4 and 5 cm in diameter were palpable. No aneurysms were convincingly felt if they were <4 cm in size. Abdominal palpation suggested a possible abdominal aortic aneurysm in ten of the 208 patients for whom ultrasonography failed to demonstrate an aneurysm.

Abdominal aortic aneurysms were significantly more likely to occur in association with aortoiliac (with or without infrainguinal) occlusive disease than with infrainguinal disease alone ($P<0{\cdot}02$, χ^2 test). Men were more likely than women to have aneurysms, and patients with aneurysms were slightly older than those without.

Sixteen patients, 11 men and five women, were found to have an ectatic aorta.

Discussion

Abdominal palpation is unreliable for diagnosing abdominal aortic aneurysm[2,8]. All aneurysms >5 cm in diameter were clinically apparent in this series, but three of ten abdominal aortic aneurysms between 4 and 5 cm in diameter were impalpable due to obesity. Aneurysms <4 cm in diameter were never convincingly felt. Abdominal ultrasonography, on the other hand, reliably detects abdominal aortic aneurysm and has a high patient acceptability.

Table 1 *Clinical data on 242 patients with occlusive peripheral vascular disease*

	Abdominal aortic aneurysm			
	Absent	Present	Size (cm)	Total
Number of patients	208	8	<3	242
		9	3–4	
		10	4–5	
		7	>5	
	Total	34		
Men	137	28		165
Women	71	6		77
Age (years)*				
Men	65 (38–87)	70 (55–86)		68 (38–95)
Women	72 (51–95)	76 (64–87)		70 (55–87)
Presenting complaint				
Claudication	158	28		186
Rest pain/ulcer	50	6		56
Site of occlusion				
Aortoiliac	31	10		41
Femoropopliteal	148	17		165
Combined segment	29	7		36

*Values are median (range)

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In this series of patients with occlusive peripheral vascular disease, 14 per cent were found to have an aneurysm on ultrasonography, half of which were >4 cm in diameter. Abdominal aortic aneurysms are often asymptomatic before rupturing, and ruptured aneurysms account for more than 3000 deaths per year in men aged >65 years in England and Wales[9]. The overall mortality rate from a ruptured aneurysm exceeds 80 per cent[10], with an operative mortality rate of around 50 per cent. On the other hand, elective operations on abdominal aortic aneurysms have a mortality rate of 5 per cent or less in specialized vascular units. Clearly, identification of abdominal aortic aneurysm before rupture is the ideal. Symptomatic aneurysms or those >5 cm in diameter should be dealt with surgically if the patient is fit, and the growth of smaller aneurysms may be carefully monitored with serial abdominal ultrasonography examinations.

Abdominal aortic aneurysms are more common in men than in women. In the present series, 17 per cent of men with peripheral vascular disease had aneurysms compared with 8 per cent of women. Furthermore, the median age of men with aneurysms was 5 years greater than that of men without aneurysm.

Screening of healthy people aged >65 years in the community results in abdominal aortic aneurysm being detected in up to 5 per cent of those screened[2,11]. A screening programme aimed only at high-risk individuals might be more cost-effective. A number of reports have confirmed that patients with peripheral vascular disease constitute such a high-risk group[5,12–14]. To date there has been no information relating the presence of an aneurysm to the distribution of occlusive disease. Patients with proximal occlusive disease appear to be at higher risk of developing an aneurysm than those with distal disease. In patients with aortoiliac disease alone, ten (24 per cent) were found to have an aneurysm compared with only 17 (10·3 per cent) patients with femoropopliteal disease. Patients with combined segment disease, above and below the inguinal ligament, had aneurysms in 7 (19 per cent) cases.

In addition to the aneurysms, 16 patients (6·6 per cent) were found to have ectatic aortas. The natural history of this condition is not fully known, but rupture may be more common than in a normal aorta[15].

Patients presenting with intermittent claudication should be carefully assessed to exclude aortic aneurysm. The older man with thigh or buttock claudication, reduced or absent femoral pulses, or iliofemoral bruits appears to be at particular risk.

References

1. Fowkes FGR, Macintyre CCA, Ruckley CV. Increasing incidence of aortic aneurysm in England and Wales. *Br Med J* 1989; **298**: 33–5.
2. Collin J, Araujo L, Walton J, Lindsell D. Oxford screening programme for abdominal aortic aneurysm in men aged 65 to 74 years. *Lancet* 1988; **ii**: 613–15.
3. Twomey A, Twomey EM, Wilkins RA, Lewis JD. Unrecognized aneurysmal disease in male hypertensive patients. *Br J Surg* 1984; **71**: 307–8.
4. Thurmond AS, Semler HJ. Abdominal aortic aneurysm: incidence in a population at risk. *J Cardiovasc Surg* 1986; **27**: 457–9.
5. Allardice JT, Allwright GJ, Wafula JMC, Wyatt AP. High prevalence of abdominal aortic aneurysm in men with peripheral vascular disease: screening by ultrasonography. *Br J Surg* 1988; **75**: 240–2.
6. Taylor LM, Porter JM. Basic data related to clinical decision making in abdominal aortic aneurysm. *Ann Vasc Surg* 1986; **4**: 502–4.
7. Collin J, Walton J. Is abdominal aortic aneurysm familial? *Br Med J* 1989; **299**: 493.
8. Beede SD, Ballard DJ, James EM, Ilstrup DM, Hallet JW. Positive predictive value of clinical suspicion of abdominal aortic aneurysm: implications for efficient use of abdominal ultrasonography. *Arch Intern Med* 1990; **150**: 549–51.
9. Office of Population Census and Surveys. *Mortality Statistics Cause 1986*. England and Wales series. DH2 13. London: HMSO, 1986.
10. Ingoldby CJH, Wajanto R, Mitchell JE. Impact of vascular surgery on community mortality from ruptured aortic aneurysms. *Br J Surg* 1986; **73**: 551–3.
11. Scott RAP, Ashton H, Kay DN. Routine ultrasound screening in management of abdominal aortic aneurysm. *Br Med J* 1988; **296**: 1079.
12. Berridge DC, Griffith CDM, Amar SS, Hopkinson BR, Makin GS. Screening for clinically unsuspected abdominal aortic aneurysms in patients with peripheral vascular disease. *Eur J Vasc Surg* 1989; **3**: 421–2.
13. Bengtsson H, Ekberg O, Aspelin P, Kallero S, Bergqvist D. Ultrasound screening of the abdominal aorta in patients with intermittent claudication. *Eur J Vasc Surg* 1989; **3**: 497–502.
14. Shapira OM, Pasik S, Wasserman JP, Barzilai N, Mashiah A. Ultrasound screening for abdominal aortic aneurysms in patients with atherosclerotic peripheral vascular disease. *J Cardiovasc Surg* 1990; **31**: 170–2.
15. Rutherford RB. Infrarenal aortic aneurysms. In: Rutherford RB, ed. *Vascular Surgery*. Philadelphia: WB Saunders, 1984: 755–71.

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Abdominal aortic aneurysm as an incidental finding in abdominal ultrasonography

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The difference between the mortality rate from ruptured abdominal aortic aneurysm (overall mortality rate 85–95 per cent and operative mortality rate 23–63 per cent), and that for elective aneurysm repair (<5 per cent) is dramatic. Awareness of the existence of an abdominal aortic aneurysm is therefore essential. Of 1800 consecutive patients aged ⩾50 years referred for their first abdominal ultrasonography, 113 who had been referred specifically for suspected abdominal aortic aneurysm or vascular screening were excluded. The remaining 1687 patients (693 men and 994 women) form the study group. Apart from the symptom-directed examination, the entire abdomen of every patient was routinely studied by ultrasonography. The definition of an abdominal aortic aneurysm was a local dilatation of the aorta with an anteroposterior diameter >30 mm or >1·5 times the anteroposterior diameter of the proximal aorta. In 82 cases (4·9 per cent) an abdominal aortic aneurysm was disclosed; 61 were in men (8·8 per cent) and 21 were in women (2·1 per cent). The prevalence of abdominal aortic aneurysm as an incidental finding in men aged ⩾60 years was 11·4 per cent. In every patient aged ⩾50 years undergoing their first abdominal ultrasonography examination, the aorta should be screened for the presence of an aneurysm.

An abdominal aortic aneurysm is potentially lethal. Its prevalence is estimated to be 1–4 per cent in the population over the age of 50 years. This prevalence is rising[1,2], even after correction for a general increased life expectancy[1,3].

The overall mortality rate from ruptured abdominal aortic aneurysm is 85–95 per cent[4]; the operative mortality rate is reported to be 23–63 per cent[5,6]. The mortality rate for elective repair, on the other hand, is <5 per cent in most centres[4,7,8]. The chances of survival for patients with an abdominal aortic aneurysm could be improved by early detection and elective surgical repair when indicated[7,9]. The long-term survival and quality of life following surgical treatment of an abdominal aortic aneurysm is comparable to that of matched population controls[9,10].

Screening for abdominal aortic aneurysms has been proven to be effective for certain risk groups as well as for the general population[4,7,11,12]. The present report concerns the detection rate of abdominal aortic aneurysms in patients over the age of 50 years undergoing their first abdominal ultrasonography examination, performed for non-vascular reasons.

Patients and methods

Between 1 September 1989 and 1 September 1990, 3055 consecutive patients aged ⩾50 years underwent abdominal ultrasonography examination in our hospital; for 1800 it was their first ultrasonography examination. Of these 1800 patients, 113 were having ultrasonography for suspected abdominal aortic aneurysm or general vascular screening and were excluded from the study. The remaining 1687 patients form the study group. According to the recommendations of the Dutch Society of Diagnostic Radiology, all patients undergoing their first ultrasonography examination, apart from a symptom-directed examination, also undergo routine screening of the entire abdomen. The ultrasonography reports of the 1687 patients were studied to ascertain those in whom an abdominal aortic aneurysm had been detected. Sex, age and maximum anteroposterior diameter of the aneurysm were recorded. Statistical analysis, using BMDP statistical software (University of California, Berkeley, California, USA), module R1 (linear regression) was performed to analyse the relationship between the diameter of the abdominal aortic aneurysm and the age of the patient.

Definition of an abdominal aortic aneurysm was a local dilatation of the aorta with an anteroposterior diameter >30 mm and/or >1·5 times the anteroposterior diameter of the proximal aorta. Measurement of the anteroposterior diameter included thrombus mass if present and was performed in the sagittal plane during systole. Excessive compression over the aorta was avoided so as not to decrease the anteroposterior diameter. All ultrasonography examinations were performed by a radiologist trained in the technique.

Results

The group of 1687 patients studied consisted of 693 men and 994 women. The mean age of the men was 66·8 (range 50–89) years and of the women was 67·4 (range 50–89) years. An abdominal aortic aneurysm was detected in 82 patients (4·9 per cent); 61 men (8·8 per cent of the male population) and 21 women (2·1 per cent of the female population). The mean age of the patients with an abdominal aortic aneurysm was 72·9 (range 51–88) years; the mean age of the men was 71·8 (range 54–88) years and of the women 75·9 (range 51–88) years (*Table 1*). The prevalence increased with age. In *Table 2* the prevalence is shown in age groups of 10 years. The prevalence of an abdominal aortic aneurysm as an incidental finding in the patients aged ⩾60 years was 6·1 per cent (men 11·4 per cent and women 2·6 per

Table 1 *Mean diameter and age of 1687 patients with an abdominal aortic aneurysm as an incidental finding*

		Abdominal aortic aneurysm			
Patients	*n*	*n*	%	Diameter (mm)	Age (years)
Men	693	61	8·8	36 (21–65)	71·8 (54–88)
Women	994	21	2·1	31 (19–45)	75·9 (51–88)
All	1687	82	4·9	35	72·9

Values in parentheses are ranges

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Table 2 *Prevalence of abdominal aortic aneurysm, according to age, as an incidental finding in abdominal ultrasonography*

	Age (years)				
Patients	50–59	60–69	70–79	80–89	All
Men	2·5	9·7	11·8	14·3	8·8
Women	0·8	0·6	2·7	6·4	2·1
All	1·5	4·2	6·6	9·2	4·9

Values are percentages

cent). The mean diameter was 35 mm for the whole group, 36 mm for men (range 21–65 mm) and 31 mm for women (range 19–45 mm) (*Table 1*). The relationship between the diameter of the abdominal aortic aneurysm and the age of the patient was analysed (*Figure 1*) but no statistically significant correlation was noted.

Discussion

The incidence of abdominal aortic aneurysm seems to be rising, even after correction for a general increase in life expectancy[1,3,9,10]. This might result from increased detection by new diagnostic methods such as ultrasonography and computed tomography, or from an increase in reported cases as effective therapy at acceptable risk has become more available. Apart from this, the condition itself might possibly have become more common[1,2]. In the literature, the prevalence is estimated to be 1–4 per cent in the population aged 50 years and older[1,10]. The mortality rate from ruptured aneurysm is high at 85–95 per cent[4]. The operative mortality rate for ruptured aneurysm is reported to be 23–63 per cent[5,6]. The mortality rate for elective surgical repair on the other hand has declined to <5 per cent in most centres[4,7,8]. The prognosis after surgical treatment (both acute and elective) with regard to life expectancy and quality of life is good, and is comparable to that of matched population controls[1,9,10,13,14].

It is obvious that to consider an elective operation, the aneurysm has to be detected. Most abdominal aortic aneurysms are diagnosed after they become symptomatic. One way to find an asymptomatic abdominal aortic aneurysm is by screening[7,11,12]. Collin *et al.*[11] found an abdominal aortic aneurysm in 5·4 per cent of 426 men aged 65–74 years in a population-based study. Scott *et al.*[12] performed a population-based study of 1404 patients aged 65–80 years in a general practice and detected an abdominal aortic aneurysm in 5·8 per cent. In the present study, an abdominal aortic aneurysm was found in 6·6 per cent of patients aged ≥65 years; considering men only, this rises to 11·8 per cent. Risk group studies have been performed among siblings of patients with an abdominal aortic aneurysm. In a group of 87 persons (32 families) aged 39–82 years, Bengtsson *et al.*[4] found an aortic dilatation in 15 per cent. Other studies of those at risk have concerned patients with peripheral vascular disease; Allardice *et al.*[8] found an abdominal aortic aneurysm and ectasia in 16 per cent of 100 consecutive patients (in 20 per cent of men and 12 per cent of women). Abdominal aortic aneurysm is reported to be four times more common in men than in women[7]; the present data yield a ratio of nearly 3:1.

This study has evaluated the prevalence of an asymptomatic abdominal aortic aneurysm in a population of 1687 consecutive patients aged ≥50 years who had a first abdominal ultrasonography examination for non-vascular reasons. In none of them was examination of the aorta specifically requested. Prevalence is influenced by the definition of an abdominal aortic aneurysm and by the composition of the group studied. Our definition implies that aneurysm has occurred when the anteroposterior diameter is >30 mm and/or >1·5 times the proximal anteroposterior diameter of the aorta. The literature lacks agreement on the definition of an abdominal aortic aneurysm. The following criteria have been used: an aortic diameter of >29 mm[4] or >30 mm[15], a diameter of >1·5 times[15,16] or >two times[12] the proximal aortic diameter or exceeding the latter by 5 mm[11]. Most publications on the subject, however, do not define an abdominal aortic aneurysm at all. Recently, the ad hoc Committee on Reporting Standards suggested the following definition: a permanent localized dilatation having at least a 50 per cent increase in diameter compared with the expected normal diameter of the artery in question[17].

Aneurysms are usually found in the elderly, rupture being an uncommon cause of death in persons under the age of 55 years[7]. The age of 50 years was chosen as the cut-off point in our study group. The overall prevalence in this group was 4·9 per cent (8·8 per cent for men, 2·1 per cent for women). In men aged ≥60 years, the prevalence was 11·4 per cent.

It is generally accepted that the risk of rupture increases as the maximal diameter of the aneurysm increases, although even small aneurysms may rupture[16]. In our hospital, elective surgical repair is considered when there is evidence of increase in the diameter of the aneurysm on consecutive ultrasonography examinations and/or when the anteroposterior diameter is >50 mm. When an asymptomatic abdominal aortic aneurysm, with a diameter of <50 mm is found, consecutive ultrasonography examinations are performed at intervals from 3 to 12 months, depending on the initial size. Intraobserver and interobserver variation may be as high as 5 mm[18]. It is important to emphasize that it is not always possible to have accurately reproducible ultrasonography measurements in every patient. For instance, in a symmetrically dilated aortic aneurysm the intraobserver and interobserver variation in measuring the anteroposterior diameter will be virtually nil. However, if the aorta is tortuous and the aneurysm has an asymmetrical and lobulated contour, variations in measurement may be considerable. To avoid misunderstanding it is important that it is stated in the ultrasonogram report whether the measurement of the anteroposterior diameter is easily reproducible (intraobserver and interobserver variation <1 mm), moderately reproducible (1–2 mm) or poorly reproducible (>2 mm). When the most reproducible diameter is found in another plane, for instance the left oblique plane, this should be mentioned in the report and recorded on hard copy images. The latter can be used for comparison during future examinations. It is our preliminary experience that approximately 15 per cent of measurements are moderately or poorly reproducible. In these patients, follow-up by computed tomography can be considered. To establish increase of the diameter it is usually necessary to compare at least three consecutive measurements. Average aneurysm diameter increase is reported to be 1·3–5 mm per year[19]. Apart from repeat ultrasonography examinations the patient should be told what to do if symptoms suggestive of imminent rupture occur.

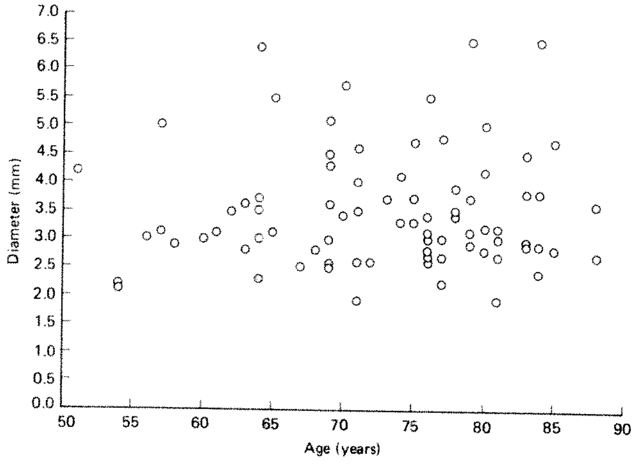

Figure 1 *Aneurysm diameter according to age*

In conclusion, it is worthwhile examining the aorta for the presence of an aneurysm in every patient over the age of 50 years undergoing abdominal ultrasonography for the first time.

References

1. Castleden WM, Mercer JC *et al.* Abdominal aortic aneurysms in Western Australia: descriptive epidemiology and patterns of rupture. *Br J Surg* 1985; **72**: 109–12.
2. Melton LJ III, Bickerstaff LK, Hollier LH *et al.* Changing incidence of abdominal aortic aneurysms: a population-based study. *Am J Epidemiol* 1984; **120**: 379–86.
3. Bickerstaff LK, Hollier LH, van Peenen HJ, Melton LJ III, Pairolero PC, Cherry KJ. Abdominal aortic aneurysms: the changing natural history. *J Vasc Surg* 1984; **1**: 6–12.
4. Bengtsson H, Norrgård Ö, Ängquist KA, Ekberg O, Öberg L, Bergqvist D. Ultrasonographic screening of the abdominal aorta among siblings of patients with abdominal aortic aneurysms. *Br J Surg* 1989; **76**: 589–91.
5. Crawford ES, Saleh SA, Babb JW III, Glaeser DH, Voccaro PS, Silvers A. Infrarenal abdominal aortic aneurysm. Factors influencing survival after operation performed over a 25-year period. *Ann Surg* 1981; **193**: 699–709.
6. Amundsen S, Trippestad A, Visite A, Søreide O *et al.* Abdominal aortic aneurysms – a national multicentre study. *Eur J Vasc Surg* 1987; **1**: 239–43.
7. Collin J. Screening for abdominal aortic aneurysms. *Br J Surg* 1985; **72**: 851–2.
8. Allardice JT, Allwright GJ, Wafula JMC, Wyatt AP. High prevalence of abdominal aortic aneurysm in men with peripheral vascular disease: screening by ultrasonography. *Br J Surg* 1988; **75**: 240–2.
9. Mutirangura P, Stonebridge PA, Clason AE *et al.* Ten-year review of non-ruptured aortic aneurysms. *Br J Surg* 1989; **76**: 1251–4.
10. Fielding JWL, Black J, Ashton F, Slaney G, Campbell DJ. Diagnosis and management of 528 abdominal aortic aneurysms. *Br Med J* 1981; **283**: 355–9.
11. Collin J, Araujo L, Walton J, Lindsell D. Oxford screening programme for abdominal aortic aneurysm in men aged 65 to 74 years. *Lancet* 1988; **ii**: 613–15.
12. Scott RAP, Ashton HA, Kay DN. Routine ultrasound screening in management of abdominal aortic aneurysm. *Br Med J* 1988; **296**: 1709–10.
13. Rohrer MJ, Cutler BS, Wheeler HB. Long-term survival and quality of life following ruptured abdominal aortic aneurysm. *Arch Surg* 1988; **123**: 1213–17.
14. van der Griend R, van Ramshorst B, Eikelboom BC. Survival and life quality after surgery for ruptured abdominal aneurysm. In: Greenhalgh RM, Mannick JA, eds. *The Cause and Management of Aneurysms.* London: Saunders, 1990: 433–40.
15. Webster MW, Ferrell RE, St. Jean PL, Majumder PP, Fogel SR, Steed DL. Ultrasound screening of first-degree relatives of patients with an abdominal aortic aneurysm. *J Vasc Surg* 1991; **13**: 9–14.
16. Cronenwett JL, Murphy TF, Zelenock GB *et al.* Actuarial analysis of variables associated with rupture of small abdominal aortic aneurysms. *Surgery* 1985; **98**: 472–83.
17. Johnston KW, Rutherford RB, Tilson MD, Shah DM, Hollier L, Stanley JC. Suggested standards for reporting on arterial aneurysms. *J Vasc Surg* 1991; **13**: 444–50.
18. Ellis M, Powell JT, Place J *et al.* The limitations of ultrasound in surveillance of small abdominal aortic aneurysms. In: Greenhalgh RM, Mannick JA, eds. *The Cause and Management of Aneurysms.* London: Saunders, 1990: 117–21.
19. Nevitt MP, Ballard DJ, Hallett JW Jr. Prognosis of abdominal aortic aneurysms. A population-based study. *N Engl J Med* 1989; **321**: 1009–14.

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Transcranial Doppler monitoring during carotid endarterectomy

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Transcranial Doppler monitoring of the middle cerebral artery blood flow velocity was used as an adjunct to routine methods of cerebral monitoring in a prospective study of 30 consecutive patients undergoing carotid endarterectomy to investigate whether transcranial Doppler monitoring provided information influencing operative technique. Application of carotid clamps caused a significant fall in middle cerebral artery velocity and there was a linear relationship between middle cerebral artery velocity and internal carotid artery stump pressure. Assuming a stump pressure of <50 mmHg to be an indication for shunting, this would correspond to a systolic middle cerebral artery velocity of <42 cm/s and a mean velocity of <30 cm/s. Transcranial Doppler monitoring immediately identified problems with shunt function and demonstrated a higher frequency of intraoperative embolization than had been anticipated, particularly after shunt insertion and final restoration of flow. With revision of operative technique this phenomenon is rarely encountered now. Two of the 30 patients exhibited a minor neurological deficit on recovery of consciousness, and transcranial Doppler monitoring was able to identify the probable underlying cause in both cases. Unnecessary and potentially hazardous re-exploration was avoided. In the absence of transcranial Doppler monitoring the neurological deficit in one of the patients might have been much worse.

Recent work from this unit[1] supports the hypothesis proposed by Sundt *et al.*[2] and Schroeder[3] that a brain with pre-existing ischaemic damage and impaired haemodynamic reserve may be more susceptible to minor embolic phenomena or apparently innocuous decreases in cerebral perfusion pressure during carotid endarterectomy. This led to a review of operative monitoring techniques to identify potentially high-risk phases of the procedure and the potential of transcranial Doppler ultrasonography[4]. Transcranial Doppler monitoring enables continuous monitoring of blood flow velocity in the middle cerebral artery during carotid surgery[5–7], has the capacity to identify intraoperative embolization[5,6] and provides on-line data on the adequacy of cerebral perfusion[7], particularly during carotid clamping.

Over the past 18 months transcranial Doppler monitoring of middle cerebral artery blood flow velocity has been used in 30 consecutive patients undergoing carotid endarterectomy to see whether the technique provided clinically useful additional information over routine methods of cerebral monitoring.

Materials and methods

A prospective study was undertaken in 30 consecutive patients undergoing carotid endarterectomy in the vascular unit of Edinburgh Royal Infirmary over an 18-month period.

Operative technique

Carotid endarterectomy was performed under normotensive, normocarbic general anaesthesia. Intravenous heparinization (3000–5000 units) was used immediately before carotid clamping, although no monitoring was undertaken of its effectiveness. The nerve to the carotid sinus was not anaesthetized or divided in any patient. Endarterectomy was performed through a longitudinal arteriotomy, care being taken to taper the distal intimal margins and, if in doubt, intimal flaps were sutured. All except one arteriotomy was closed with a saphenous vein patch.

Operative monitoring

Systemic blood pressure and heart rate were monitored continuously from a radial artery cannula and electrocardiogram. End-tidal CO_2 was maintained within the range 32–40 mmHg. In all patients, the adequacy of internal carotid artery backflow was assessed subjectively; backflow was deemed to be 'good' if flow was brisk and pulsatile, 'moderate' if flow was brisk but non-pulsatile, and the remainder were classified as 'poor'. Internal carotid artery stump pressure was measured in 24 patients by direct needle puncture (connected to a pressure transducer) with the common and external carotid arteries clamped. Cerebral electrical activity was monitored with a cerebral function monitor but this malfunctioned repeatedly towards the latter part of the study. A temporary indwelling shunt (Javid or Pruitt–Inahara) was employed in 15 patients using the following criteria: (1) cerebral function monitor abnormality; (2) poor internal carotid artery backflow; (3) internal carotid artery stump pressure <50 mmHg.

Monitoring of middle cerebral artery blood flow velocity

Systolic and mean blood flow velocity in the main stem of the ipsilateral middle cerebral artery were measured in the manner described by Aaslid[8], using the EME TC2-64B transcranial Doppler (Eden Medical Electronics, Uberlingen, Germany) through the transtemporal cranial window. In the majority of patients a hand-held probe was used, but recently a headpiece holding the ultrasonography probe in position has been used. Before any measurement, the probe was adjusted until the maximum flow signal was obtained when it was assumed that the angle of insonation of the ultrasonography beam to the middle cerebral artery was as close to zero as possible, and that the perceived velocity obtained from the Doppler shift was equal to the absolute velocity[4]. Every minute during each phase of the procedure, recordings of systolic and mean middle cerebral artery velocity, systemic blood pressure, heart rate and end-tidal CO_2 were made. End-tidal CO_2 was measured because of the known dependency of middle cerebral artery velocity on the arterial partial pressure of CO_2[9]. These parameters were also assessed 1 day before operation in all patients.

Statistical analysis

Middle cerebral artery velocity, blood pressure and end-tidal CO_2 were not normally distributed (Filliben's test)[10] and non-parametric tests of analysis were used. Values in the text and tables refer to the median and its 95 per cent confidence limits. Statistical significance was assessed using the Wilcoxon signed rank (paired data) and the Mann–Whitney tests (non-paired data). A P value of ≤ 0.05 was taken to represent a statistically significant result. Recordings were made every minute but for the purposes of analysis the operation was divided into six phases:

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preoperative, induction (first 5 min after establishment of stable anaesthesia), preclamp (period of carotid mobilization), clamp (during carotid clamping), shunt, and postclamp (following final restoration of flow).

Results

Intraoperative changes in middle cerebral artery velocity

The median values (with 95 per cent confidence limits) for systolic and mean middle cerebral artery velocity, mean arterial pressure and end-tidal CO_2 during the operation are detailed in *Table 1*. Compared with the preoperative data, middle cerebral artery velocity did not change significantly after induction of anaesthesia. As expected, both systolic and mean middle cerebral artery velocity decreased significantly after carotid clamping (*Figure 1a*), but returned to normal levels in those in whom a shunt was employed (*Figure 1b*). In three patients, there was no significant decrease in middle cerebral artery velocity following clamping and all had internal carotid artery stenoses in excess of 80 per cent. Preoperative transcranial Doppler monitoring studies had shown reversed flow in the ipsilateral anterior cerebral artery, indicating recruitment of the collateral circulation.

Correlation between middle cerebral artery velocity and internal carotid artery stump pressure and backflow

There was a linear relationship between systolic and mean middle cerebral artery velocity and internal carotid artery stump pressure after carotid clamping (*Figure 2a* and *b*). If an internal carotid artery stump pressure of <50 mmHg is assumed to be an indication for shunting, regression analysis shows this to correspond to a systolic middle cerebral artery velocity of 42 cm/s and a mean middle cerebral artery velocity of 30 cm/s. Three patients had no detectable middle cerebral artery flow after carotid clamping. All had poor internal carotid artery backflow with stump pressures of 0, 0 and 20 mmHg, respectively. *Table 2* details the relationship between middle cerebral artery velocity and internal carotid artery stump pressure compared with subjective analysis of internal carotid artery backflow at the time of clamping. Although there was a

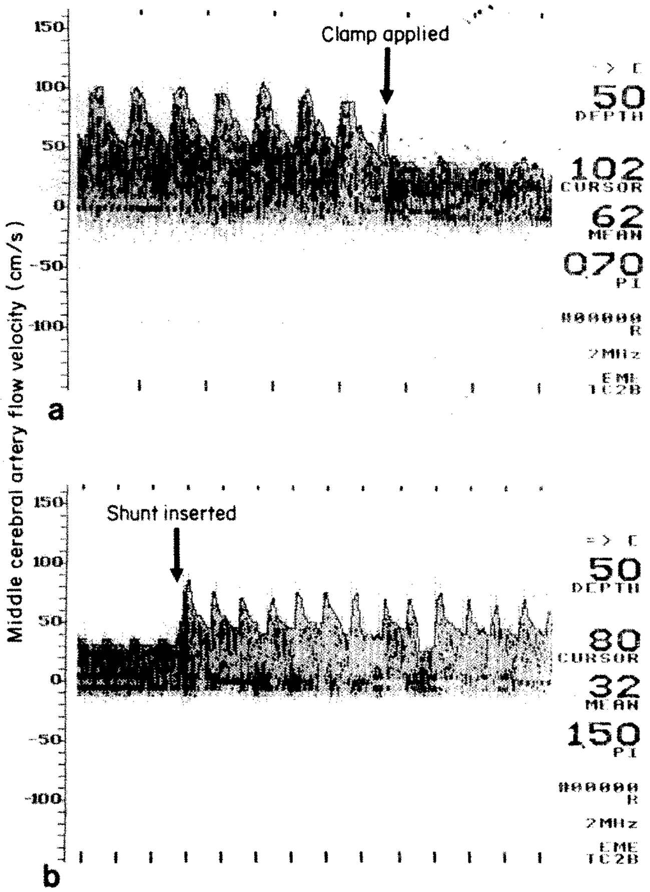

Figure 1 *Reduction in middle cerebral artery flow velocity* **a** *following application of the carotid clamp, and* **b** *restoration of normal velocity waveform following shunt insertion*

Table 1 *Systolic and mean middle cerebral artery velocity, mean arterial pressure and end-tidal CO_2 during carotid endarterectomy*

	Systolic velocity (cm/s)	Mean velocity (cm/s)	Mean arterial pressure (mmHg)	End-tidal CO_2 (mmHg)
Preoperative	75 (67–80)	47 (43–51)	100 (96–107)	38 (36–40)
Induction	71 (64–79)	49 (44–55)	80 (76–85)*	36 (35–37)
Preclamping	78 (70–87)	56 (50–62)†	89 (84–94)*	36 (35–37)
Clamp	46 (37–57)*	35 (28–42)*	96 (90–103)	36 (35–37)
Shunt	66 (60–75)	48 (44–54)	86 (79–93)*	36 (35–37)
Postclamping	105 (96–116)*	73 (66–79)*	87 (83–92)*	38 (37–39)

Values are median (95 per cent confidence limits). $*P < 0{\cdot}0001$ (compared with admission baseline data); $\dagger P < 0{\cdot}005$ (compared with admission baseline data)

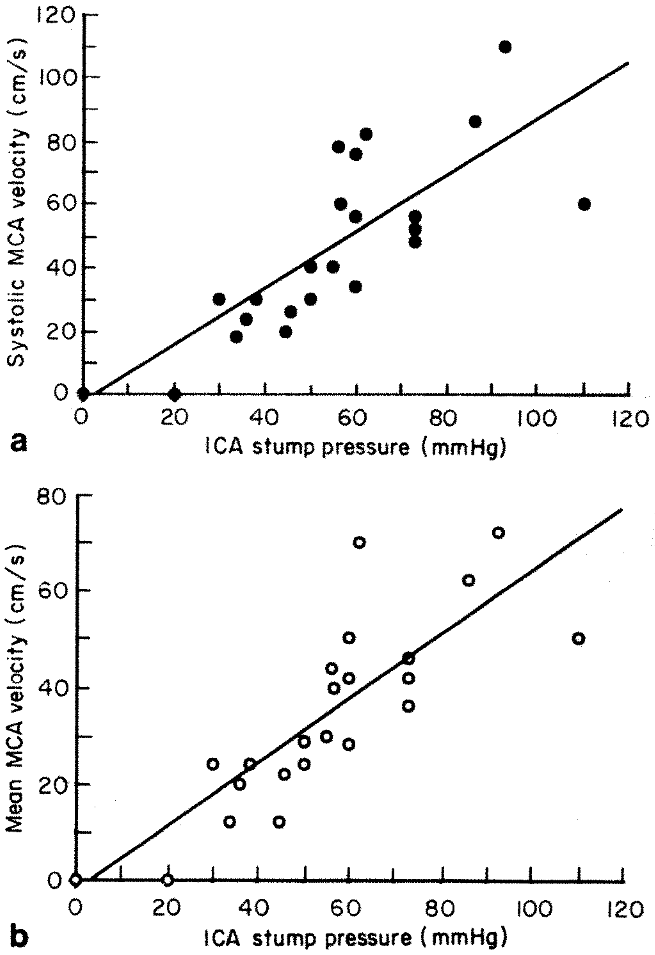

Figure 2 *Relationship between* **a** *systolic middle cerebral artery (MCA) velocity and* **b** *mean middle cerebral artery velocity with internal carotid artery (ICA) stump pressure following carotid clamping. Systolic middle cerebral artery velocity* $= -3{\cdot}2 + 0{\cdot}89$ *stump pressure* ($r = 0{\cdot}81$, $P < 0{\cdot}0001$). *Mean middle cerebral artery velocity* $= -2{\cdot}4 + 0{\cdot}66$ *stump pressure* ($r = 0{\cdot}85$, $P < 0{\cdot}0001$)

Table 2 *Correlation between median middle cerebral artery velocity and median internal carotid artery stump pressure with analysis of internal carotid artery backflow following carotid clamping*

	Assessment of internal carotid artery backflow		
	Good ($n = 11$)	Moderate ($n = 9$)	Poor ($n = 10$)
Systolic velocity (cm/s)	60 (42–81)	45 (33–58)	19 (5–30)
Mean velocity (cm/s)	44 (32–58)	34 (26–42)	12 (4–24)
Systolic internal carotid artery stump pressure (mmHg)	73 (56–92)	58 (42–66)	25 (7–41)

Values are median (95 per cent confidence limits)

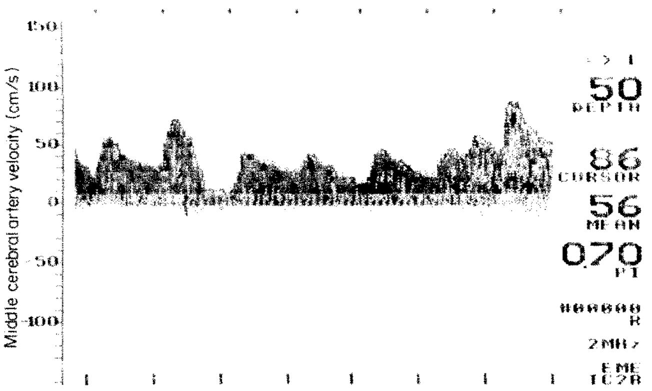

Figure 3 *Distortion of the middle cerebral artery velocity waveform during carotid mobilization*

trend for velocity and stump pressure to be higher in patients with good, as opposed to moderate, backflow the difference was not statistically significant. Patients with good or moderate internal carotid artery backflow had significantly higher middle cerebral artery velocity ($P < 0{\cdot}001$) and internal carotid artery stump pressure ($P < 0{\cdot}002$) than patients with poor internal carotid artery backflow.

Practical implications of transcranial Doppler monitoring during carotid endarterectomy

A number of practical points of interest emerged as a consequence of the use of transcranial Doppler monitoring. In most patients, carotid mobilization (particularly when slings were passed around the carotid bifurcation) caused a significant distortion of the ensuing middle cerebral artery waveform (*Figure 3*) and in one patient there was transcranial Doppler monitoring evidence of embolism into the middle cerebral artery during this phase. Although some degree of carotid manipulation cannot be avoided, the surgeon should remain aware that patients with a friable or thrombotic plaque are susceptible to embolization at this time.

A transcranial Doppler monitoring diagnosis of intra-operative embolism (air/platelet) was made when a high-pitched, 'chirping' signal was detected and manifest on the middle cerebral artery waveform as a bidirectional signal[5,6]. This phenomenon is clearly distinguishable from the grating, artefactual sound of probe movement. Embolization occurs as a discrete event (*Figure 4a*) or as a run of bidirectional signals which may completely obscure the underlying waveform. *Figure 4b* illustrates multiple emboli through the middle cerebral artery following insertion of a shunt into the external carotid artery and restoration of flow (internal carotid artery chronically occluded). This example clearly demonstrates that the external carotid artery may be an important source of collateral flow to the brain via reversed flow in the ipsilateral ophthalmic artery. Fifteen patients had transcranial Doppler monitoring evidence of embolism; it was observed in one patient during carotid mobilization, in one during carotid clamping, in 12 immediately after shunt insertion and restoration of flow and in eight following final clamp release and restoration of flow. Awareness of these features has led to even greater care in flushing the shunt before insertion, and of the arteriotomy site before clamp release, with the result that this problem has subsequently rarely been seen.

The decision to use a shunt was based on a stump pressure of <50 mmHg, poor backflow, or a cerebral function monitor abnormality in 14 of the 15 patients who required a shunt. In the remaining patient, systolic middle cerebral artery velocity after clamping was initially 60 cm/s (stump pressure 60/40 mmHg, good internal carotid artery backflow) and no shunt was used. At 12 min after clamping, systolic middle cerebral artery velocity fell to 40 cm/s and backflow was poor. A shunt was inserted and systolic flow velocity was restored to 70 cm/s. One particularly useful application of transcranial Doppler monitoring has been in monitoring middle cerebral artery velocity flow during shunting. In one patient, two episodes of defective flow caused by inadvertent kinking of a Javid shunt were immediately detected and rectified. In a second patient, the middle cerebral artery signal after insertion of a Pruitt–Inahara shunt was noted to be poor. Partial deflation of the distal (internal carotid artery) balloon and repositioning of the shunt led to rapid signal improvement. In the absence of transcranial Doppler monitoring, these shunt problems might have gone unnoticed.

Two patients were found, on recovering from anaesthesia, to have minor transient neurological deficits. Transcranial

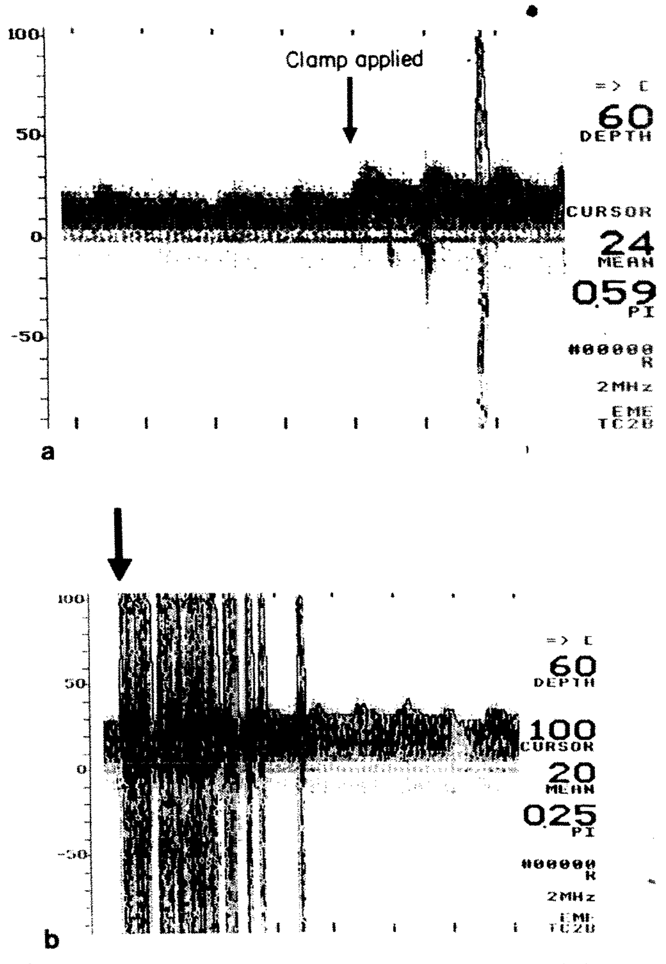

Figure 4 *Transcranial Doppler evidence of intraoperative embolization.* **a** *Discrete emboli following clamp release and final restoration of flow.* **b** *Stream of emboli following restoration of flow through a shunt inserted into the external carotid artery. The point of flow release is indicated by the arrow*

Doppler monitoring suggested a probable cause in both. In one, satisfactory middle cerebral artery velocity flow was observed after carotid clamping, but 5 min later, the signal suddenly disappeared. After shunt insertion, the middle cerebral artery flow signal returned. These findings suggested occlusion of the middle cerebral artery (by embolism or *in situ* thrombosis) during carotid clamping, with subsequent fragmentation and distal propagation of the thrombus after shunt insertion. A postoperative computed tomography (CT) scan showed no evidence of haemorrhage. In the absence of transcranial Doppler monitoring, the abrupt cessation of flow in the middle cerebral artery would not have been identified, the requirement for urgent shunting missed and the first indication of any serious problem might have been the detection of an abnormality on the cerebral function monitor or the discovery of a neurological deficit after operation. In the second patient, application of the carotid clamps caused middle cerebral artery velocity to fall to zero. This was observed in three patients, although in two middle cerebral artery velocity progressively increased to 20–30 cm/s indicating recruitment of the collateral circulation. In the third patient, middle cerebral artery velocity remained at zero throughout the period of clamping until a shunt was inserted, whereupon normal velocity flow was restored. No emboli were detected during the operation. After recovery from anaesthesia, the patient had a minor monoparesis from which he fully recovered within 2 h. A postoperative CT scan showed no evidence of haemorhage. These observations suggest an underlying haemodynamic cause.

The discovery of a neurological deficit in these two patients raised the possibility of internal carotid artery occlusion. Previously, immediate carotid re-exploration would have been undertaken. In both situations, transcranial Doppler monitoring was able to demonstrate excellent flow in the symptomatic middle cerebral artery and internal carotid artery (the latter via insonation through the transorbital window), and re-exploration was avoided.

Discussion

If transcranial Doppler is a useful means of cerebral monitoring during carotid endarterectomy it must provide clinically useful information not available by other methods. The attraction of transcranial Doppler monitoring is not that it demonstrates the logical and inevitable changes in middle cerebral artery velocity during each phase of the procedure, but rather, it is the unpredictable phenomena that are the most interesting[5–7] and of the most practical importance. Neurophysiological techniques provide important information on ischaemic injury after a period has elapsed since the underlying event. They cannot differentiate between a haemodynamic and embolic pathophysiology and the potential of transcranial Doppler monitoring is to provide warning of developing problems before cerebral ischaemia gives rise to changes in electroencephalogram evoked potential.

The introduction of transcranial Doppler monitoring has not altered the basic criteria for shunting. The capability for continuous monitoring makes possible the identification of declining velocity and therefore a decrease in cerebral perfusion during the period of clamping. A shunt should be inserted if the systolic velocity falls below 40 cm/s or the mean velocity below 30 cm/s. This relatively arbitrary threshold is based on regression analysis and corresponds to a systolic stump pressure of 50 mmHg (*Figure 2*). Halsey *et al.*[7] showed that ipsilateral electroencephalogram suppression occurred when mean middle cerebral artery velocity fell below 15 cm/s. The new threshold provides considerable reserve, recognizing that the relationship between stump pressure and cerebral blood flow is not always linear and predictable[11] and that the critical perfusion threshold in patients with a preoperative CT scan infarct or ischaemic neurological deficit may be much higher than in normal subjects.

The introduction of transcranial Doppler monitoring has helped in other ways; it has heightened awareness of potentially dangerous phases of the operation. Mobilization of the carotid bifurcation is often associated with significant distortion of the middle cerebral artery waveform[5] and if the underlying plaque is friable or thrombotic it is susceptible to embolization. The high incidence of air/platelet embolization during shunt insertion and after restoration of flow was surprising. This type of embolization may be minor but recent evidence suggests that it may be a potentially important source of morbidity[6]. An already haemodynamically compromised brain, or one with an area of infarction as shown by CT scan, is likely to be more susceptible to 'innocuous embolic phenomena' than a normal brain[1] and any amendment of operative technique to decrease embolization is encouraged.

An important aspect of this study was that in three patients, transcranial Doppler monitoring provided important information that significantly influenced management. This is particularly relevant to the patient who suffered acute occlusison of the middle cerebral artery during clamping. During carotid clamping, the velocity of blood flow in the ipsilateral cerebral arterial compartment almost always decreases and it has been suggesed that this could delay the passage and subsequent fragmentation of emboli and thereby increase the risk of superimposed thrombus formation[12]. Insertion of a shunt presumably fragmented the embolus with subsequent dispersion in the distal vessels. In the absence of transcranial Doppler monitoring the middle cerebral artery occlusion would not have been noted and the resultant neurological deficit would almost certainly have been much more serious. Transcranial Doppler monitoring was able to confirm patency of the middle cerebral artery and internal carotid artery syphon in the recovery room in the two patients suffering a neurological deficit, thus avoiding the need for immediate re-exploration to exclude thrombosis of the operated segment[13]. The other two patients in whom transcranial Doppler monitoring provided important information had shunt malfunctions that were immediately recognized and corrected. Without transcranial Doppler monitoring, it is likely that any subsequent neurological deficit would be attributed incorrectly to embolization.

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References

1. Naylor AR, Merrick MV, Ruckley CV. Risk factors for intra-operative neurological deficit during carotid endarterectomy. *Eur J Vasc Surg* 1991; **5**: 33–9.
2. Sundt TM, Sharbrough FW, Piepgras DG, Kearns TP, Messick JM, O'Fallon WM. Correlation of cerebral blood flow and EEG changes during carotid endarterectomy. *Mayo Clin Proc* 1981; **56**: 533–43.
3. Schroeder T. Haemodynamic significance of internal carotid artery disease. *Acta Neurol Scand* 1988; **77**: 353–72.
4. Aaslid R, Markwalder T-M, Nornes H. Non-invasive transcranial ultrasound recording of flow velocity in basal cerebral arteries. *J Neurosurg* 1982; **57**: 769–74.
5. Padayachee TS, Gosling RG, Bishop CC, Burnand K, Browse NL. Monitoring middle cerebral artery velocity during carotid endarterectomy. *Br J Surg* 1986; **73**: 98–100.
6. Spencer MP, Thomas GI, Nicholls SC, Sauvage LR. Detection of middle cerbral artery emboli during carotid endarterectomy using transcranial Doppler ultrasonography. *Stroke* 1990; **21**: 415–23.
7. Halsey JH, McDowell HA, Gelmon S, Morawetz RB. Blood flow velocity in the middle cerebral artery and regional cerebral blood flow during carotid endarterectomy. *Stroke* 1989; **20**: 53–8.
8. Aaslid R. Transcranial Doppler examination techniques. In: Aaslid R, ed. *Transcranial Doppler Sonography*. Vienna: Springer, 1986: 39–59.

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Oxerutins in the prevention of recurrence in chronic venous ulceration: randomized controlled trial

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The value of oxerutins [O-(β-hydroxyethyl)-rutosides] in the prevention of venous ulcer recurrence was investigated in a double-blind randomized controlled trial of 138 patients with recently healed chronic venous ulcers. Oxerutins in the form of Paroven 500 mg twice daily or identical placebo were given, and all patients were provided with elastic compression stockings. At follow-up 3 months later, patients were assessed for re-ulceration and for tablet and stocking compliance. Oxerutins ($n=69$) *and placebo* ($n=69$) *groups were well matched for age, sex, duration of previous ulceration and deep vein thrombosis. Cumulative re-ulceration by life-table analysis at 12 and 18 months was 22 and 32 per cent respectively for placebo, and 23 and 34 per cent respectively for oxerutins* ($P=0{\cdot}93$). *Recurrence was more frequent in patients who complied with both tablets and stockings, suggesting that compliance was influenced by continued symptoms* ($P=0{\cdot}006$). *This trial failed to demonstrate that oxerutins influenced ulcer recurrence.*

Chronic venous ulcer presents a massive problem, with over 100 000 ulcers treated in the UK at any one time[1]. Venous ulcers heal intermittently and then recur repeatedly over many years. Adequate compression achieves healing of most ulcers, but recurrence is frequent and has been reported to affect 49 per cent of patients at 3 months and 69 per cent at 1 year after healing[2,3]. Prevention of this recurrence is the key to successful overall management of these unfortunate and usually elderly patients.

Venous ulceration results from persistently elevated venous pressures caused by venous incompetence or obstruction, failure of the calf muscle pump, immobility and obesity. Tissue oedema follows capillary transudation of fluid resulting from an elevated venous pressure and may promote the deposition of protein molecules within the subcutaneous tissue with the formation of the pericapillary fibrin cuff identified by Browse and Burnand[4]. This fibrin cuff, the inevitable oedema or capillary damage by leucocytes causes a diffusion block which reduces tissue oxygenation, leading ultimately to ulceration[5]. A reduction in both capillary pressure and capillary transudation could be expected to have long-term effects on ulcer recurrence.

Oxerutins [O-(β-hydroxyethyl)-rutosides] given orally have been demonstrated to reduce capillary leakage in both healthy volunteers and in patients with chronic venous insufficiency, although the mechanism of action remains obscure[6,7]. Symptoms of venous insufficiency such as aching, cramps and eczema have also been reported to be relieved with oxerutins[8,9]. Oxerutins significantly increase the low tissue oxygen pressure found in the gaiter area of patients with chronic venous insufficiency[10–12]. There are few known side-effects, and interaction with other drugs has not been reported[13]. Oxerutins are already being widely prescribed as prolonged therapy in this elderly group of patients in the belief that they reduce oedema, fibrin deposition and ulcer recurrence.

This double-blind controlled clinical trial was designed to evaluate the influence of oxerutins on ulcer recurrence in patients with recently healed venous ulcers.

Patients and methods

This was a randomized double-blind trial of oxerutins in 138 patients with a recently healed chronic venous ulcer. Patients were recruited following informed consent at their first follow-up appointment within 1 month of healing by graduated high compression bandaging in the Charing Cross Venous Ulcer Research Clinic. Patients with arterial disease detected by an ankle:brachial pressure index of $<0{\cdot}8$ were excluded. Below-knee graduated elastic stockings (Class II) were fitted in all patients, with instructions to wear these throughout the day. Following a detailed venous assessment, including ambulatory venous pressure measurements, 48 patients were recommended to have surgery to correct superficial venous incompetence. These patients were included in the trial but were randomized by a separate code to ensure equal distribution between the treatment groups.

Randomization and drug therapy

Patients were randomized to equal groups of 69 taking either oxerutins in the form of Paroven (Zyma, UK) 500 mg twice daily or identical placebo tablets. The drugs were supplied directly by the hospital pharmacy and neither patient nor investigator was aware of their nature.

Follow-up and analysis of results

Each patient was reviewed at a special 'healed ulcer' clinic at intervals of 3 months. Drug and stocking compliance was assessed by tablet counts and direct enquiry. Elastic stockings fitted in the clinic were replaced when necessary and a new supply of tablets provided. The date of any ulcer recurrence was recorded and the patient then returned to the Venous Ulcer Research Clinic for compression bandaging.

Results were analysed on an 'intention to treat' basis with no withdrawals or exclusions. Ulcer recurrence was assessed by the life-table method using the log rank test of significance. Presenting data and symptoms were compared between oxerutins and placebo groups using the standard normal deviate comparison of proportions. A sample size of 120 patients was calculated on the assumption that the recurrence rate of 50 per cent could be reduced by 20 per cent by the addition of oxerutins (power = 80 per cent, $P=0{\cdot}05$).

Results

Two groups, each of 69 patients, were randomized for patient and ulcer characteristics (*Table 1*).

The overall cumulative probability of recurrence was 22·5 per cent at 12 months, increasing to 33 per cent by 18 months. There was no difference in ulcer recurrence between the patients randomized to oxerutins or placebo (*Figure 1*). By 1 year the cumulative recurrence on oxerutins was 23 per cent compared with 22 per cent on placebo. By 18 months recurrence

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Table 1 *Comparison between patients randomized to oxerutins or placebo*

	Oxerutins	Placebo	*P*
Mean age in years (s.e.m.)	66·5(1·6)	68·2(1·4)	0·10
Mean ulcer duration in months (s.e.m.)	8·9(1·4)	8·8(1·7)	0·32
Men (%)	30 (44)	25 (36)	0·35
Women (%)	39 (56)	44 (64)	
Diabetics (%)	4 (6)	4 (6)	1·00
Congestive cardiac failure (%)	5 (7)	8 (12)	0·38
Previous deep venous thrombosis (%)	11 (16)	10 (14)	0·81
Steroid therapy (%)	0 (0)	2 (3)	0·15

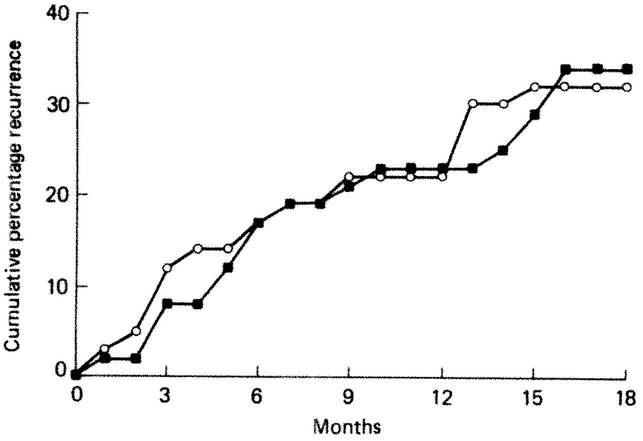

Figure 1 *Percentage cumulative recurrence is plotted by life table and demonstrates no difference between patients treated with oxerutins (■) and placebo (○) (P = 0·93)*

had increased to 34 per cent on oxerutins and 32 per cent on placebo. This small difference was not statistically significant when analysed by the log rank method (*P* = 0·93).

Drug compliance had little or no effect; there were 13 of 40 (33 per cent) recurrences in those taking their tablets, compared with 5 of 33 (15 per cent) recurrences in those not taking their tablets (*P* = 0·13).

Generally, compliance with the wearing of elastic stockings was good in these patients, with 96 of 138 wearing their stockings for >75 per cent of the day. The recurrence rate tended to be lower at 6 per cent in patients who discontinued wearing stockings compared with 36 per cent in the 'good' compliers (*P* = 0·06).

There were 89 patients who took their tablets and wore their stockings (good compliers) and 48 who did not. *Figure 2* shows that at 18 months, 43 per cent of the good compliers had re-ulcerated compared with 15 per cent of the poor compliers (*P* = 0·006).

Discussion

The overall cumulative recurrence rate of 22·5 per cent in the first year of this trial was substantially lower than previously reported but it was not influenced by oxerutins[3]. We believe that recurrence was low because of close supervision and the careful fitting of elastic stockings. This explanation may seem strange in view of the higher recurrence rates in patients who consistently wore their stockings. This trend in favour of poor compliance was also true for taking tablets and it is possible that patients only consistently wore stockings and took tablets if they had symptoms to suggest that recurrent ulceration was likely. Those patients with few symptoms, and presumably less severe venous insufficiency, may have stopped treatment because they felt well. Clearly the role of elastic stockings cannot be evaluated from the results of this trial and it has not been possible to identify any randomized trials in the literature.

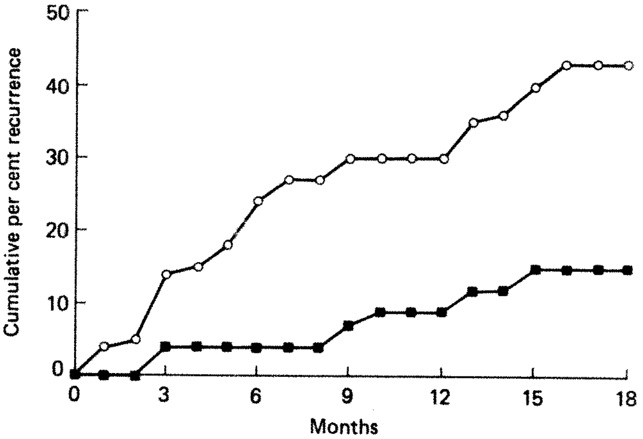

Figure 2 *Cumulative ulcer recurrence comparing good (○) and poor (■) compliance for drugs and the wearing of stockings* (P = *0·006*)

While rapid healing of venous ulcers is important, a more positive approach to prevention of ulcer recurrence is required. If the substantially reduced ulcer recurrence in this study was not the result of carefully fitted and supervised compression stockings and regular follow-up, then we have no explanation for these results. The addition of oxerutins had no significant effect on the risk of re-ulceration.

Acknowledgements

This project was supported by Zyma (UK) Ltd.

References

1. Dale JJ, Callum MJ, Ruckley CV, Harper DR, Barrey PN. Chronic ulcers of the leg: a study of prevalence in a Scottish community. *Health Bull (Edinb)* 1983; **41**: 310–14.
2. Blair SD, Wright DDI, Backhouse CM, Riddle E, McCollum CN. Sustained compression and healing of chronic venous ulcers. *Br Med J* 1988; **297**: 159–61.
3. Monk BE, Sarkany I. Outcome of treatment of venous stasis ulcers. *Clin Exp Dermatol* 1982; **7**: 397–400.
4. Browse NL, Burnand KG. The cause of venous ulceration. *Lancet* 1982; **i**: 243–5.
5. Byrne P, Naughton PM, O'Higgins NJ. Transcutaneous oxygen tension (*P*tc O_2) in the lower limbs in venous disease. *Br J Surg* 1984; **71**: 990.
6. Roztocil K, Perovsky I, Oliva I. The effect of hydroxyethyl-rutosides on capillary filtration rate in the lower limb of man. *Eur J Clin Pharm* 1977; **11**: 435–8.
7. Bergqvist D, Hallbook T, Lindblad B, Lindhagen A. A double blind trial of o-(β-hydroxyethyl)-rutosides in patients with chronic venous insufficiency. *Vasa* 1981; **10**: 253–60.
8. Balmer A, Limoni C. A double blind placebo controlled clinical trial of Venoruton on the symptoms and signs of chronic venous insufficiency. The importance of patient selection. *Vasa* 1980; **9**: 76–82.
9. Pulvertaft TB. General practice treatment of symptoms of venous insufficiency with oxerutins. Results of a 660 patient multicentre study in the UK. *Vasa* 1983; **12**: 373–6.
10. Burnand K, Powell S, Bishop C, Stacey M, Pulvertaft T. Effects of Paroven on skin oxygenation in patients with varicose veins. *Phlebology* 1989; **4**: 15–22.
11. Neumann HAM, van der Broek NJ. A double blind trial of the influence of (beta-hydroxyethyl) rutosides on the P_{tcO_2} and light reflection rheography in patients with chronic venous insufficiency. *Phlebology* 1991 (in press).
12. Belcaro G, Rulo A, Candiani C. Evaluation of the micro-circulatory effects of Veruton in patients with chronic venous hypertension by laser Doppler flowmetry, transcutaneous PO_2 and PCO_2 measurements, leg lumetry and ambulatory venous pressure measurements. *Vasa* 1989; **18**: 146–51.
13. Casley-Smith JR, Casley-Smith JR. *High Protein Oedemas and the Benzo-Pyrones.* 1986, Sydney, Baltimore: Lippincott.

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Br. J. Surg. 1991, Vol. 78, October, 1271–1272

Prospective audit of vascular surgical emergencies in a District General Hospital

A prospective clinical audit was carried out to assess the volume and distribution of workload generated by vascular surgical emergencies over a 3-month period in a single health district in the UK. Of 53 consecutive patients referred as surgical emergencies with peripheral vascular problems, 45 were referred to a single vascular surgeon, 36 directly from a general practitioner or other specialist and nine from another general surgeon. A total of 39 operations and six radiological procedures were carried out, including 26 vascular reconstructions. To accommodate the 27 non-urgent operations, nine were performed 'out of hours' and 17 planned cases were cancelled. A median of five general surgical beds were required throughout the period studied and 11 patients required intensive therapy unit admission for a total of 39 days. It is concluded that vascular surgical emergencies constitute a substantial workload and are being dealt with mainly by a single vascular surgeon who effectively works a one in one rota. Inadequate facilities for urgent vascular surgery lead to a large number of cases being dealt with out of hours and frequent cancellation of routine operations.

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Specialization within general surgery continues to excite controversy. A number of subspecialties are already recognized and have their own examinations and training. There is a continuing trend towards greater specialization[1], although there are some who consider this undesirable[2]. As more elective surgery is carried out by specialists, problems may arise in the management of emergencies. The larger centres with many surgeons may be able to maintain a number of specialist 'on call' rotas, but this is rarely feasible in a District General Hospital. The recent confidential enquiry into perioperative deaths (CEPOD) report[3] suggested that many of the identifiable failures of management occurred in the more difficult, out of hours, emergency surgery. There must, therefore, be the fear that increasing specialization for elective work will lead to reduced ability to deal with such emergencies.

Vascular surgery is already a separate specialty in many countries[4]. The development of new techniques, which may require complex facilities and specialized support staff, makes it increasingly difficult for the non-specialist. Previous audits of vascular surgery in the UK have originated mainly from vascular units in teaching hospitals[5,6], while the majority of vascular surgery in the UK is carried out by general surgeons with a special interest[7]. A previous study from this unit has shown that vascular surgical patients occupy a greater proportion of beds and theatre time than their general surgical counterparts[8]. A prospective audit has been undertaken to assess the way in which vascular surgical emergencies are referred and dealt with in a single health district and to quantify the demands which they impose on general surgical facilities.

Patients and methods

West Berkshire Health Authority serves a population of approximately 450 000 people. The general surgical service is provided by six consultant surgeons based at two hospitals in Reading. General surgical emergencies, including acute vascular and urological cases, are accepted on a one in six 'on call' rota. One of the surgeons has a major interest in vascular surgery and a second carries out a small number of elective vascular procedures (less than ten per year). The other surgeons have special interests which include gastroenterology, breast and endocrine surgery, and none of them undertakes elective vascular surgery.

All elective vascular surgery is carried out at the Royal Berkshire Hospital where there are 56 adult general surgical beds shared between four surgeons. The hospital has a six-bed intensive therapy unit, currently staffed for four beds, and no high dependency unit. There is a comprehensive vascular radiology service, including provision for urgent angioplasty and thrombolysis.

From 1 September to 30 November 1990 a prospective audit was carried out of all patients with a vascular diagnosis who were referred as an emergency to any of the general surgeons for an opinion or admission. The source, time and nature of referral was recorded along with full details of all subsequent investigations and management, and of transfers or consultations between surgeons.

Results

Over the 3-month period, 53 patients were referred. The primary vascular diagnoses were as shown in *Table 1* with the majority of patients having acute (seven cases) or ruptured (seven cases) aneurysms, acutely ischaemic limbs (seven lower limb, four upper limb) or ulcerated or gangrenous extremities (21 cases).

Most of the patients with aneurysms and acutely ischaemic limbs, 20 of 25, presented to the surgeon on duty, the others being referred directly to the vascular surgeon even though he was not on call. Ten patients presented urgently to a surgeon who did not carry out elective vascular surgery; one underwent femoral embolectomy by the registrar on call, one with a ruptured aneurysm was transferred to a different hospital, and operation was considered inappropriate for another. The remaining seven patients were transferred to the care of the vascular surgeon immediately (four cases) or the following day (three cases) without previous treatment.

The largest group of patients comprised 21 with ulceration or gangrene from peripheral vascular disease (ten with diabetes

Table 1 *Final diagnosis of 53 emergency vascular referrals*

Diagnosis	Number
Ruptured abdominal aortic aneurysm	7
Painful abdominal aortic aneurysm	7
Acute lower limb ischaemia	7
Acute upper limb ischaemia	4
Foot ulceration/gangrene	21
Deep venous thrombosis or venous gangrene	4
Vascular access	2
Amaurosis fugax	1

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Table 2 *Procedures performed on emergency vascular referrals*

Procedure	Number
Abdominal aortic aneurysm repair	11
Aortobifemoral graft	1
Aortobifemoral with femoropopliteal graft	1
Femoral embolectomy	4
Brachial embolectomy	2
Iliopopliteal graft	1
In situ femoropopliteal vein graft	2
Exploration of pedal vessels	1
Creation of arteriovenous fistula	2
Carotid endarterectomy	1
Wound debridement	3
Toe amputation	4
Transmetatarsal amputation	1
Below-knee amputation	2
Above-knee amputation	3
Balloon angioplasty	2
Intra-arterial thrombolysis	4

mellitus). Two of these patients were admitted by the on call surgeon and transferred to the vascular surgeon the following day. All of the others were referred directly to the vascular surgeon by a general practitioner (12 cases) or physician (seven cases).

Thirty-nine operations and six radiological procedures were carried out on these patients (*Table 2*). Of the operations performed, there were 12 emergency (comprising four aneurysms, six embolectomies and two bypass grafts) and 14 scheduled vascular reconstructions, along with 13 debridements or amputations. Nine of the scheduled operations were not able to be accommodated on routine lists and were carried out in the evening or at the weekend. The 18 that were carried out on routine lists resulted in the cancellation of 17 planned operations (including three elective aneurysm repairs, one aortobifemoral bypass, four femoropopliteal bypasses and nine general cases). Nineteen patients underwent intravenous digital subtraction angiography, of which four were performed outside office hours. In four patients with acute ischaemia, thrombolysis was carried out as the primary treatment.

Median inpatient stay was 7 days (range 0–42 days) and there was a median of five beds (range two to ten beds) occupied by patients with vascular emergencies throughout the period of the study, with numbers altering quickly over short periods (*Figure 1*). The four patients admitted as an emergency who underwent a major amputation (one bilateral) required a total of 124 bed days. Eleven patients required a total of 39 days in the intensive therapy unit, with a median stay of 2 days; a maximum of three intensive therapy unit beds were occupied simultaneously.

Discussion

These data illustrate that although there is no official cover for vascular surgery, the vast majority of vascular surgical emergencies are dealt with by one vascular surgeon who effectively works close to a one in one rota. This is not an uncommon situation; a recent survey by the Vascular Surgical Society of Great Britain and Ireland showed that 23 per cent of respondents provided one in one cover for vascular surgery and 30 per cent a one in two cover[7].

The two main reasons for emergency vascular admissions requiring urgent surgery are aneurysm and acute ischaemia. The overall number of patients in this series treated for these conditions is similar to that predicted from other studies[5]. There is evidence that the results of surgery for ruptured aneurysm are better in the hands of a specialist vascular surgeon[9] and that treatment of acute ischaemia is best undertaken in a specialist unit[10]. A survey carried out by the Vascular Surgical Society showed that although 55 per cent of general surgeons who were not members of the Society did some vascular surgery, over 60 per cent of them did less than ten elective operations each year; a similar number did less than ten emergency cases each year (Ruckley CV. Report on Questionnaire Surveys 1988–9. Vascular Surgical Society of Great Britain and Ireland Newsletter). The increasing use of specialist techniques and growth in litigation may make it progressively more difficult for vascular patients to be treated by non-specialists.

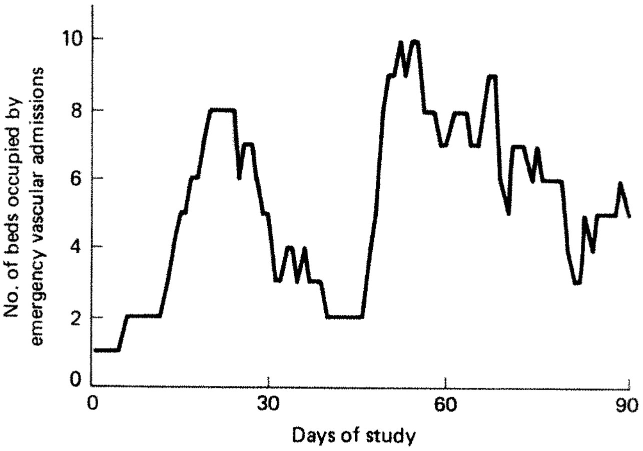

Figure 1 *Number of general surgical beds occupied by vascular surgical emergencies during the study period*

The workload generated by emergency vascular referrals is substantial and unpredictable. This leads to frequent cancellation of planned admissions. Furthermore, a considerable number of non-urgent operations in the present series had to be performed outside scheduled operating lists. This is contrary to the recommendations of the CEPOD report which stressed the importance of having adequately staffed and equipped facilities for scheduling urgent surgery within working hours[3].

Although vascular cases accounted for only about 10 per cent of total surgical emergencies during the period of the study, they produced a disproportionate workload and made considerable demands in terms of usage of general and intensive therapy unit beds, radiological facilities and operating theatre time. For these demands to be met, a high level of flexibility is required which is difficult with current pressures aimed at increasing efficiency. The facilities required in Reading to cope with the emergency vascular workload would be approximately one intensive therapy unit, five general beds and about half a day of operating theatre time (4 h) each week. Were these facilities available, the vascular surgery workload could be dealt with without resorting to the cancellation of scheduled cases or performing non-urgent cases out of hours.

References

1. Johnson CD. Specialisation in general surgery. *Health Trends* 1990; **22**: 37–9.
2. Irving M. The general surgeon. *Br Med J* 1986; **292**: 741–2.
3. Buck N, Devlin HB. The report of the confidential enquiry into perioperative deaths. London: Nuffield Provincial Hospitals Trust, Kings Fund, 1987.
4. Muller-Wiefel H. Vascular surgery – what is the future? *Eur J Vasc Surg* 1990; **4**: 1–3.
5. Campbell WB, Souter RG, Collin J, Wood RFM, Kidson IG, Morris PJ. Auditing the vascular surgical audit. *Br J Surg* 1987; **74**: 98–100.
6. Roberts J, Smallwood JA, Chant ADB, Webster JHH. Local audit in vascular surgery. *Ann R Coll Surg Engl* 1990; **72**: 287–90.
7. Ruckley CV. Mounting problems in vascular surgery. *Br Med J* 1988; **297**: 577–8.
8. Jaffe J, Chadwick L, Tomkins M, Galland RB. General surgeons with a special interest in vascular surgery: an audit of relative workload. *Ann R Coll Surg Engl* (in press).
9. Ouriel K, Geary K, Green RM, Fiore W, Geary JE, DeWeese JA. Factors determining survival after ruptured aneurysm: the hospital, the surgeon and the patient. *J Vasc Surg* 1990; **11**: 493–6.
10. Clason AE, Stonebridge PA, Duncan AJ, Nolan B, Jenkins AMcL, Ruckley CV. Acute ischaemia of the lower limb: the effect of centralizing vascular surgical services on morbidity and mortality. *Br J Surg* 1989; **76**: 592–3.

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Correspondence

Results of a recently instituted programme of thrombolytic therapy in acute lower limb ischaemia

Sir

I should like to comment on two points made in the recent paper by Mr K. J. Dawson and colleagues (*Br J Surg* 1991; **78**: 409–11). It is probably right to suggest that 'rTPA is superior to other commonly used thrombolytic agents' in peripheral thrombolysis. However, the view that 'this is broadly in agreement with the literature reported for coronary thrombolysis' is questionable. The findings of the TIMI (thrombolysis in myocardial infarction) study were not reflected in the much larger GISSI-2 study[1] which used objective clinical end points.

With regard to complications, the contention that 'It is the failure of treatment to achieve successful lysis rather than the duration of infusion which is important' is not justified by the results in this paper, in which a small group of patients were studied and in which all complications were considered as one. I would not dispute that rethrombosis and amputation are related to the failure of treatment but am reluctant to accept that the risk of major haemorrhage is not increased by the unnecessary prolongation of the thrombolytic infusion. Haemorrhagic complications and, particularly, haemorrhagic strokes are perhaps the greatest fear of clinicians using peripheral thrombolysis; it would be particularly regrettable for one to occur in a patient in whom clinical clearance had already occurred and the thrombolytic infusion was being run overnight simply to maintain patency because angiography was not available until the following morning.

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1. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarcto miocardico. GISSI-2: a factorial randomized trial of alteplase *versus* streptokinase and heparin *versus* no heparin among 12 490 patients with acute myocardial infarction. *Lancet* 1990; **336**: 65–71.

Authors' reply

Sir

We would like to respond to the two points made by Mr R. Lonsdale about our recent article.

We agree that the cardiological literature no longer supports the contention that rTPA is superior to streptokinase for treatment of myocardial infarction, as indicated by the GISSI-2 study and preliminary results of the ISIS-3 (Third International Study on Infarction Survival) study. These comprehensive trials were reported after our article was submitted and so we were unable to be influenced by their conclusions. The relevance of these conclusions to intra-arterial, low dose, local infusions must, however, be questioned.

The second point, concerning complications, needs to be considered in several ways. Mr Lonsdale's concerns are that our policy may increase haemorrhagic complications. This is a legitimate worry and one which would cause us to alter our existing arrangements were it so. We have recently presented work to the Vascular Society of Great Britain and Ireland on minimizing groin haemorrhage with the use of catheter sheaths[1], and showed that our rate of haemorrhagic complications, from all causes, was the same overall as that generally experienced in the world literature[2]. Using our present protocol that incidence of haemorrhage has now decreased in our current experience of 80 patients. Angiography is available around the clock at our unit but we choose to perform follow-up angiography during routine hours so as to maximize the number of experienced radiological and surgical staff present. We feel that this has been beneficial in terms of both the opinions available and the quality of study performed. As we understand the system at Nottingham, angiography in these patients is performed on the wards by non-radiological staff. This obviously works well for that particular unit, facilitated by the presence of a full-time vascular research fellow dealing with thrombolysis. This situation is unlikely to pertain in other units, and we consider it important that a system is evolved which is clinically feasible and practical in most institutions as we believe that thrombolysis will become widespread and routine. We feel our approach achieves this goal and that the theoretical risk of increased haemorrhage complications has not become clinically evident.

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1. Dawson K, Dex E, Platts A, Hamilton G. Groin haemorrhage complicating intra-arterial thrombolytic therapy: choice of technique and agent. *Br J Surg* 1991; **78**: 363–4 (Abstract).
2. Berridge DS, Makin GS, Hopkinson BR. Local low dose intra-arterial thrombolytic therapy: the risk of stroke or major haemorrhage. *Br J Surg* 1989; **76**: 1230–3.

Specialization in general surgery

Sir

In his leading article (*Br J Surg* 1991; **78**: 259–60) Mr C. D. Johnson defined general surgery as the residue of surgical practice that remains after the separation of the major surgical specialties and is convinced that, although its area has been shrinking for many years, it will continue to exist. He inevitably kept disappointingly to this narrowing brief, and at no point did he mention the concomitant shrinking of general medicine. There is increasing dependence on doctors who are not trained surgeons in dealing with what were surgical complexities in two of the three major areas of subspecialization (gastroenterology and endocrinology, as Johnson puts it) that remain after the shrinkage away from general surgery or neurosurgery, orthopaedics and cardiothoracic surgery.

Against this development, I now argue that the trend, where surgery is involved, must be for the major clinical departments to be departments of gastroenterology and endocrinology, as well as departments of neurology, cardiology and chest diseases, obstetrics and gynaecology, paediatrics, orthopaedics, urology, vascular disease and so on. This process entails the disappearance of heads of departments, and, in the long run, of professors of general medicine and surgery in the larger district hospitals and university hospitals. Such departments should allow better teaching of students and training of would-be consultant surgeons, besides the bonus, from time to time at least, of more expert management of patients. Johnson agrees that surgeons will practice in one or more 'subspecialties' and 'restrict their "general" surgical activity to intermediate cases and the provision of emergency cover'. The Association of Surgeons has already found that future vacancies in hospitals will almost always be filled by surgeons with special interests.

The disappearance of general surgery by the development of departments will allow the same plan of training, as discussed by Johnson, for those surgeons who are appointed to hospitals that do not have specialist departments. As a university surgeon I found it most helpful to be able to hold my outpatient clinics at the same time as the medical gastroenterologists and endocrinologists, as well as to go often on their relevant 'medical' ward rounds. This arrangement was undoubtedly helped by the more flexible timetable of my appointment, and may not often be easily possible for National Health Service consultants not part of a specialist department.

Johnson concludes that 'general surgery has a future, but this future requires increasing subspecialization'. That seems to amount to hedging and appears to go against what, to me, in retirement, should be beneficial departmentalism.

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Major trauma: a district general hospital experience

Sir

Ingham Clark and Tabone-Vassallo are to be congratulated on their advocacy of the establishment of trauma teams with Advanced Trauma Life Support (ATLS) training (*Br J Surg* 1991; **78**: 230–3), but their contention that trauma care in the district general hospital is as good as that in the teaching hospital is of no comfort. The Royal College of Surgeons' studies on death from injury showed marked deficiencies in the care provided in either type of hospital[1]. The authors correctly point out inadequacies in TRISS, although this methodology is better suited to prospective study of considerably larger numbers of patients for the purposes of local audit and for comparison between centres as in the Major Trauma Outcome Study.

The establishment of trauma teams, the members of which should have undergone ATLS training, should be a current priority but the limitations must be recognized. These teams maximize existing resources and reduce the chance of management errors occurring by removing the prospect of an untrained junior struggling alone with a patient with multiple injuries. However, team composition is continually changing, and this does little to encourage the accumulation of specific expertise within an institution to allow improvements in the management of the complex case. This situation contrasts with the trauma centre which, by virtue of its greater case load, dedicated resources and the particular interests of its staff, will allow the development of management systems able to investigate and treat the patient with multiple injuries more rapidly and completely than at present. It appears that about half of all potentially avoidable deaths from injury result not from missed injuries or wrong treatments, but from an accumulation of the effects of several moderate injuries, the treatment of which has not been as rapid as would be ideal. Improvements in the outcome of these cases may require more frequent involvement with major trauma than would appear to happen in the district general setting from the figures presented in this paper.

The development of trained hospital trauma teams has much to commend it, but they should not be seen as an adequate substitute for the development of trauma centres.

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1. Anderson ID, Woodford M, De Dombal FT, Irving M. Retrospective study of 1000 deaths from injury in England and Wales. *Br Med J* 1988; **296**: 1305–8.

Authors' reply

Sir

Mr Anderson suggests in his letter that surgical trainees would receive much better experience in the treatment of patients with major injuries if they trained in a trauma centre rather than a district general hospital. A recent study from a level 1 trauma centre in Dallas[1] suggests that this is not the case. Surgical residents in this centre carried out an average of 97 operations for major trauma during their 5-year training period. The authors of this study also calculated that the cost of non-payment of bills for treatment of trauma patients in their centre worked out at 1·5 million dollars per surgical resident!

Trauma centres will not necessarily provide better training for surgeons in Britain, and it is unlikely that the National Health Service could afford to run such centres.

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1. Roye WP Jr, Dunn EL, Watermeyer DS, Gossard WH. Postgraduate trauma education: the surgeon, the cost. *J Trauma* 1989; **29**: 1471–5.

Spontaneous abdominal arteriovenous fistulae

Sir

We read with interest the paper by Gilling-Smith and Mansfield (*Br J Surg* 1991; **78**: 421–6) describing their experience with aortocaval fistulae. However, we were disappointed that our paper on the subject[1] was not quoted in their review of the English literature.

Our report detailed the presentation and management of two cases that were diagnosed preoperatively. We also reported three further cases where an aortocaval fistula was diagnosed at operation; these were not presented in detail.

In our first patient, control of blood loss on opening the sac was achieved using Foley catheters passed from inside the aortic aneurysm across the fistula into the superior and inferior vena cava. In the second patient, venous thrombectomy catheters were passed up the femoral veins before laparotomy and the balloons inflated before opening the aneurysm. Control of blood loss was poor using this technique – almost certainly related to the size of balloon catheters that were available.

Although they describe the use of balloon occlusion catheters in their paper, it is not clear of what type these were and how they were inserted. Were remotely inserted venous occlusion catheters[2] used and, if so, were any difficulties encountered with the procedure?

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1. Duffy JP, Gardham JRC. Spontaneous aortocaval fistula – preoperative diagnosis and management. *Postgrad Med J* 1989; **65**: 397–9.
2. Smith SRG, Mansfield AO, Bradley JPW. Remotely inserted venous occlusion catheters for the control of venous haemorrhage. *Ann R Coll Surg Engl* 1988; **70**: 161–2.

Authors' reply

Sir

We thank Messrs Duffy and Gardham for their interest in our paper.

We employ Fogarty balloon occlusion catheters (Edwards Laboratories) with either 10 ml (iliac vein) or 43 ml (vena cava) balloons. These are placed in the inferior vena cava and/or iliac veins at the start of the procedure via the long saphenous vein or one of its tributaries in the groin[1]. Balloons are not inflated until the fistula has been exposed when they can be repositioned to obtain maximum control of venous haemorrhage. We have not encountered any difficulties with this technique.

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1. Smith SRG, Mansfield AO, Bradley JBW. Remotely inserted venous occlusion catheters for the control of venous haemorrhage. *Ann R Coll Surg Engl* 1988; **70**: 161–2.

Interstitial hernia: a report of four cases in infants

Sir

Messrs Drake and Biswas (*Br J Surg* 1990; **77**: 906–7) have reported four cases in which there was an intermittent groin swelling, ipsilateral impalpable testes (in three) and a hernial sac which extended only as far as the external ring. Both their clinical and operative descriptions in the three boys are consistent with intracanalicular testes, a variant of undescended testes which is well recognized by paediatric surgeons. This explains why their 'hernias' were always associated with ipsilateral crypto-orchidism. To label this condition on the evidence they provide as an example of the so-called 'interstitial hernia' is misleading and inaccurate. In the true interstitial hernia the hernial sac goes in an abnormal direction between the layers of the muscles: in the cases described there is little to suggest that this has occurred, apart from their impression as to where the internal ring may have lain (we suspect they may not appreciate how far lateral to the external ring it is situated).

It is interesting to note that there is not one reference to modern paediatric surgical literature. Indeed, despite the enormous combined knowledge of paediatric surgeons around the world, it is not described in the major paediatric surgical text[1]. It is of concern to us that the signs may have been misinterpreted by the authors.

We do acknowledge, however, that most hernias in infants pass through the external ring, and are not limited to the inguinal canal: the findings described are those of a widely patent processus vaginalis with an undescended testis; the treatment of this condition is orchidopexy and not herniotomy.

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1. Welch KJ, Randolph JG, Ravitch MM, O'Neill JA, Rowe MI. *Paediatric Surgery*. 4th ed. Chicago: Year Book Medical Publishers, 1986.

Authors' reply

Sir

Messrs Beasley and Hutson are correct in emphasizing that 'in the true interstitial hernia the hernial sac goes in an abnormal direction'. In the four reported cases the hernial sac presented clinically with a bulge lateral to and above the internal inguinal ring. Operative findings confirmed that in each case the neck of the hernia was at the internal ring but the sac extended upwards and laterally.

The lack of recent reports in the surgical literature prompted us to publish these cases in a journal with a wide surgical readership.

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Laparoscopic cholecystectomy and the common bile duct

Letter 1

Sir

We read with interest the leading article by McEntee, Grace and Bouchier-Hayes (*Br J Surg* 1991; **78**: 385–6) which mentioned intravenous cholangiography (IVC) for visualization of the common bile duct (CBD) before laparoscopic cholecystectomy. During the past 15 years it has been our normal practice to perform this investigation about 2 weeks before cholecystectomy in all non-jaundiced patients. In our experience IVC has been safe and, with added tomography, produces good definition of the CBD, sufficient to judge its calibre and the presence or absence of calculi within. In a very small minority of cases the image quality has been too poor for a confident judgement on the state of the CBD to be made. In these patients a peroperative cholangiogram has been performed. We are not aware of any patient with a stone-free preoperative CBD who has suffered choledocholithiasis after cholecystectomy. Our patients have not been reviewed formally because the most appropriate method of assessment would be a second IVC, a difficult study to justify.

For many years surgeons have wanted an image of the CBD in patients requiring cholecystectomy. The method advocated with great force was peroperative cholangiography to the exclusion of other techniques. We believe that IVC has several advantages and, with the advent of laparoscopic cholecystectomy, merits wider adoption. Endoscopic retrograde cholangiography can be reserved for cases where the IVC has not given a good enough image. Surgeons performing laparoscopic cholecystectomy may want to avoid peroperative cholangiography: preoperative IVC is worth their consideration.

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Letter 2

Sir

Bouchier-Hayes and colleagues at Dublin, in their leading article, appear to advocate the omission of peroperative cholangiography at laparoscopic cholecystectomy in those in whom common duct stones are not suspected. They base this radical suggestion on the basis of only 1 per cent of problems from retained common duct stones following laparoscopic cholecystectomy over a very short period. They may well be right, but it is unwise to extrapolate over the next 20 years on their short experience.

My experience is much shorter even than theirs, but I have found that operative cholangiography at laparoscopic cholecystectomy is usually possible. Its value is not only in the detection of common duct stones, but also in defining the anatomy of the common duct, thereby ensuring ligation of the cystic duct at the appropriate position.

Laparoscopic cholecystectomy must entail a risk of damage to the common duct while one is on the learning curve, and thus operative radiography is even more important.

What is needed are improved methods of obtaining cholangiography, followed by effective methods of dealing with retained stones at laparoscopy. While Bouchier-Hayes should be encouraged to set up a prospective study under scientific conditions of omission of cholangiography, the rest of us should be encouraged to continue with the practice of the last 20 years which was based on sound principles, and experience.

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Authors' reply

Sir

We thank Mr Weston Underwood for his comments following our leading article in the *Journal* recently. We have never denied that laparoscopic peroperative cholangiography was possible in the majority of patients and the current literature would indicate that cholangiograms can be obtained easily in 75–80 per cent of cases[1]. However, we question the need for routine cholangiography. We agreed with Yip *et al.*[2] that the prevention of biliary injury is best achieved by meticulous identification of the biliary anatomy, especially at Calot's triangle, before division of any important structure rather than relying solely on operative cholangiography. Indeed, we are aware of at least one duct injury which was sustained *after* a normal cholangiogram had been obtained. Whether asymptomatic common duct stones require any treatment awaits further elucidation and we hope to be able to comment on this point at a later date.

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1. Reddick EJ, Olsen DO. Laparoscopic laser cholecystectomy. *Surgical Endoscopy* 1989; **3**: 131–3.
2. Yip ACW, Ng WS, Chow WC, Choi TK, Lam KH. Plea for selective operative cholangiography. *J R Coll Surg Edinb* 1991; **36**: 21–4.

Laparoscopic cholecystectomy

Sir

Laparoscopic cholecystectomy enjoys the dubious distinction of being the only operation to have attracted more editorials and leading articles than reported series. In this light, the points raised by Mr Paterson-Brown and his colleagues (*Br J Surg* 1991; **78**: 131–2) are valid, but we feel that the training aspects of laparoscopic surgery need to be addressed more practically. It is not enough simply to state that patient welfare 'must not be jeopardized' and that progress up the learning curve should be measured; the question is how?

We agree wholeheartedly with the view that all surgical trainees should acquire laparoscopic skills. In the future laparoscopic techniques will be taught and learned by the time honoured 'man and boy' principle. This practice has served well in the past and is the way in which surgical and endoscopic skills are learned today. At present the problem is that there are not enough 'men'.

Professors Cuschieri and Berci, in their book on laparoscopic cholecystectomy[1], list requirements for the development of laparoscopic skills. Professor Berci, writing in the *American Journal of Surgery*[2], further details the steps that surgeons should take to become 'properly trained' for laparoscopic surgery. Reddick[3] supports such proposals and outlines the progress required before embarking on laparoscopic cholecystectomy. Concrete proposals are the need for comprehensive instruction on the principles and equipment and the use of laparoscopic simulators or benchtop trainers to develop the manipulative skills and depth perception. These then are the minimum skills required before proceeding to an animal model. All authors agree that the use of a live animal model is essential before progressing to human laparoscopic cholecystectomy. There is no short cut. For the trained surgeon to develop laparoscopic skills *at no cost to the patient*, he must be able to perform the procedures successfully in animals. These then are some of the measurements on the learning curve. There will be objections to the use of animals in this way, but there is no need for the animals to be killed and, as your editorial states, 'patient welfare must not be jeopardized'.

At the Prince of Wales Hospital, Chinese University of Hong Kong, laparoscopic cholecystectomy is now the treatment of choice for symptomatic gallstone disease and laparoscopic surgical procedures are increasingly used for other surgical problems. We are keenly aware of the problems of training both juniors and experienced surgeons in laparoscopic techniques. We have devised a series of exercises to be practised on simulators. Three to four hours of such exercises enables novice laparoscopists to overcome the initial problems of coordination and depth perception. We feel that animal surgery is then essential to 'iron out the wrinkles' in the technique and also to develop new laparoscopic procedures for clinical practice. It is our firm belief that such training is essential for those surgeons otherwise experienced in biliary surgery who wish to perform laparoscopic cholecystectomy on man.

If laparoscopic surgery is to carry us into the next surgical generation, we must develop new techniques and refine instrumentation. Although this is possible in the clinical setting, progress will be, at best, sedate. The only limitations to laparoscopic surgery are imagination, instrumentation and training. Imagination is not lacking among the profession and instrumentation is advancing faster than ever. Can training keep up? In their report on the Dundee experience[4], Professor Cuschieri and his colleagues suggest that 'training implications on a national scale will impose logistic problems'. The logistic problem of bringing the current generation of surgeons up to date is most urgent. It behoves centres with established programmes of laparoscopic cholecystectomy to offer training. Training courses with simulators, live animal models and closed circuit television demonstrations will help plumb the depths of laparoscopic inexperience. We need to train the trainers quickly and raise laparoscopic knowledge and level of skill in order that such surgery be practised safely, and be fully developed as a practical alternative to open operation at no cost to the patient.

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S. C. S. Chung
A. K. C. Li

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1. Cuschieri A, Berci G. *Laparoscopic Biliary Surgery*. Oxford: Blackwell Scientific Publications, 1990: 1.
2. Berci G. Editorial. *Am J Surg* 1990; **160**: 488–9.
3. Reddick EJ. Editorial. *Am J Surg* 1990; **160**: 488.
4. Nathanson LK, Shimi S, Cuschieri A. Laparoscopic cholecystectomy: the Dundee technique. *Br J Surg* 1991; **78**: 155–9.

Editors' note

Mr Sunderland and colleagues argue that it is essential to develop laparoscopic operating skill in an animal model before performing this procedure in patients. Readers should establish the legality of such a course in their own country before embarking on this path. In the UK, the Animals (Scientific Procedures) Act 1986 allows only one exception to the use of animals for the purpose of acquiring surgical skills: terminally anaesthetized rodents may be used by qualified surgeons on approved training courses on microsurgery. All other uses of animals for the purpose of acquiring surgical skills are illegal under this Act.

This question has been considered at the Joint Meeting of Surgical Colleges, January and April 1991. It is the Colleges' view that the use of pigs or other animals to train surgeons in laparoscopic cholecystectomy could not be justified.

The Royal College of Surgeons of England has issued guidance[1] to surgeons who are planning to undertake laparoscopic cholecystectomy. This guidance makes the recommendation that basic laparoscopic operative skills should be acquired initially in bench training sessions using inanimate material.

There appears to be no case for making laparoscopic surgery an exception to the time-honoured methods for acquiring new surgical skills. These involve a full understanding of the theoretical considerations, bench work with inanimate or cadaver material, and observation of and instruction by surgeons skilled in the technique.

1. Royal College of Surgeons of England. *Minimal Access Surgery. Laparoscopic Cholecystectomy and Related Gastrointestinal Procedures*. London, 1990.

Regeneration of the spleen and splenic autotransplantation

Sir

In the review on splenic reimplantation (*Br J Surg* 1991; **78**: 270–8) complications are reported to be few. The situation may well be different in tropical Africa, and we draw attention to our experience in Zambia, where we began carrying out splenic reimplantation following splenectomy for isolated splenic trauma during the period 1988–1990. Complications occurred in the second patient for one of us and in the fourth patient for the other.

One 15-year-old boy suddenly developed acute intestinal obstruction on the eighth postoperative day as the result of adhesions of the small bowel to a small abscess around a splenic implant into the omentum. Another small abscess had simultaneously formed around a second implant placed in the splenic bed. The second patient, a 25-year-old man, developed a large abscess at the site of a splenic implant into an extraperitoneal pouch of the splenic bed. This abscess was drained on the tenth postoperative day, and the implants were removed.

The bacteriology in neither case is known. Both patients had normal-looking spleens and both appeared to have been in previous good health. The adult had no antibodies to human immunodeficiency virus (Wellcozyme Eliza).

We cannot explain these complications. We can only postulate reduced immunity, perhaps as a result of widely prevalent malaria, subclinical malnutrition or a higher background of prevailing infection and bacteraemia.

Neither of us has attempted further reimplantation following this experience.

C. Bem
D. Echun

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Notices and announcements

20–25 October 1991
American College of Surgeons Annual Clinical Congress
Chicago, USA
Information: Sally Gerneski, American College of Surgeons, 55 East Erie Street, Chicago, Illinois 60611–2797 USA

30 Oct–3 Nov and 3 Nov–6 Nov 1991
International Conference of Gastroenterology
Hong Kong then Beijing, China
Information: Conference Secretariat, 12/F Kaiseng Commercial Centre, 4–6 Hankow Road, Kowloon, Hong Kong

30 October–3 November 1991
Course/Workshop in Blood Vessel Imaging Using Ultrasound Techniques
Torquay, UK
Information: Mr K. N. Humphries, Blood Vessel Imaging Course, 10 Swale Drive, Chandlers Ford, Hampshire SO5 3QY, UK

5–8 November 1991
Intensive Practical Course in Phlebology
Houston, Texas, USA
Information: N.A.S.P., 204 N. El Camino Real, E-234, Encinitas, CA 92024, USA

7 November 1991
'Vascular Training Would Be Improved By A Specific Diploma'
London, UK
Information: Mr John Wolfe, Secretary, London Vascular Debating Group, St. Mary's Hospital, London, W2 1NY, UK

7–9 November 1991
3rd Combined Meeting of the Nederlandse Vereniging voor Thoraxchirurgie and the Deutsche Gesellschaft für Thorax-, Herz- und Gefässchirurgie
Maastricht, The Netherlands
Information: Organizing Secretariat, Conference Agency Limburg, University Hospital Maastricht, PO Box 1918, 6201 BX Maastricht, The Netherlands

7–10 November 1991
XVII European Society for Medical Oncology Conference
Lyon, France
Information: Michel Clavel, MD, XVII Congress ESMO, CLB, 28 Rue Laennec, 69373 Lyon Cedex 08, France

8 November 1991
Vascular Symposium. Angioplasty, Thrombolysis and Angioscopy – A Minimally Invasive Approach to Arterial Disease
Edinburgh, UK
Information: Sheila Heap, Meadox (UK) Ltd., Matthew House, Matthew Street, Dunstable, Bedfordshire LU6 1SD, UK

12–14 November 1991
1st European Conference on Tissue Banking and Clinical Application
Berlin, Germany
Information: Mr Rudiger von Versen, German Central Tissue Bank, ITT, Medical Faculty (Charite), Humboldt-University Berlin, Schumannstr. 20/21, D-1040 Berlin, Germany

14–16 November 1991
10th Annual WBAMC Trauma Symposium
El Paso, Texas, USA
Information: Mrs Marty May, Trauma Service/SICU, Department of the Army, William Beaumont Army Medical Center, El Paso, Texas 79920–5001, USA

15–16 November 1991
Laparoscopic Cholecystectomy Workshop
Edinburgh, UK
Information: Mrs Maureen Webb, Royal College of Surgeons of Edinburgh, Nicolson Street, Edinburgh EH8 9DW, UK

17–23 November 1991
Surgery of the Pancreas, Liver and Biliary System
Edinburgh, UK
Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

19–22 November 1991
7th International Symposium on Cardiopulmonary Urgencies and Emergencies
Rotterdam, The Netherlands
Information: Dr O. Prakash, University Hospital Rotterdam, dr. molewaterplein 40, 3015 GD Rotterdam, The Netherlands

3–5 December 1991
6th International Workshop on Therapeutic Endoscopy
Hong Kong
Information: Dr J. W. C. Leung, Department of Medicine, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong

12–13 December 1991
1st EEC Conference on Pain Research
Brussels, Belgium
Information: M. Staquet, Rue Heger-Bordet, 1, B-1000 Brussels, Belgium

13 December 1991
Section of Surgery of the Royal Society of Medicine Teaching Day
Sheffield, UK
Information: Postgraduate Centre, Northern General Hospital, Herries Road, Sheffield S5 7AU, UK

5–8 January 1992
Postgraduate Gastroenterology Course
Oxford, UK
Information: Dr D. P. Jewell, Radcliffe Infirmary, Oxford OX2 6HE, UK

17–19 January 1992
XXVIII Head and Neck Course
Liverpool, UK
Information: Mrs B. Cowley, Department of Otorhinolaryngology, University of Liverpool, Royal Liverpool Hospital, PO Box 147, Liverpool L69 3BX, UK

30 January 1992
'Graft Infection – the Hidden Problem'
London, UK
Information: Mr John Wolfe, Secretary, London Vascular Debating Group, St. Mary's Hospital, London W2 1NY, UK

1–3 April 1992
Association of Surgeons of Great Britain and Ireland Annual Meeting
Jersey
Information: Ms Caroline Ross, The Royal College of Surgeons, 35/43 Lincoln's Inn Fields, London WC2 3PN, UK

22–25 April 1992
2nd International Workshop and Symposium on Therapeutic Endoscopy and Gastroenterology
Shanghai, China
Information: Dr Joseph Yeung, Department of Medicine, Prince of Wales Hospital, Shatin, Hong Kong

3–7 May 1992
7th International Congress on Senology (Breast Diseases) of the Senologic International Society
Rhodes, Greece
Information: Congress Secretariat, 102 Michalakopoulou Street, GR-115 28 Athens, Greece

10–16 May 1992
Acute Trauma Management
Belfast, UK
Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

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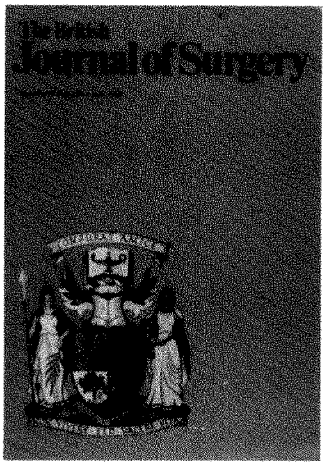

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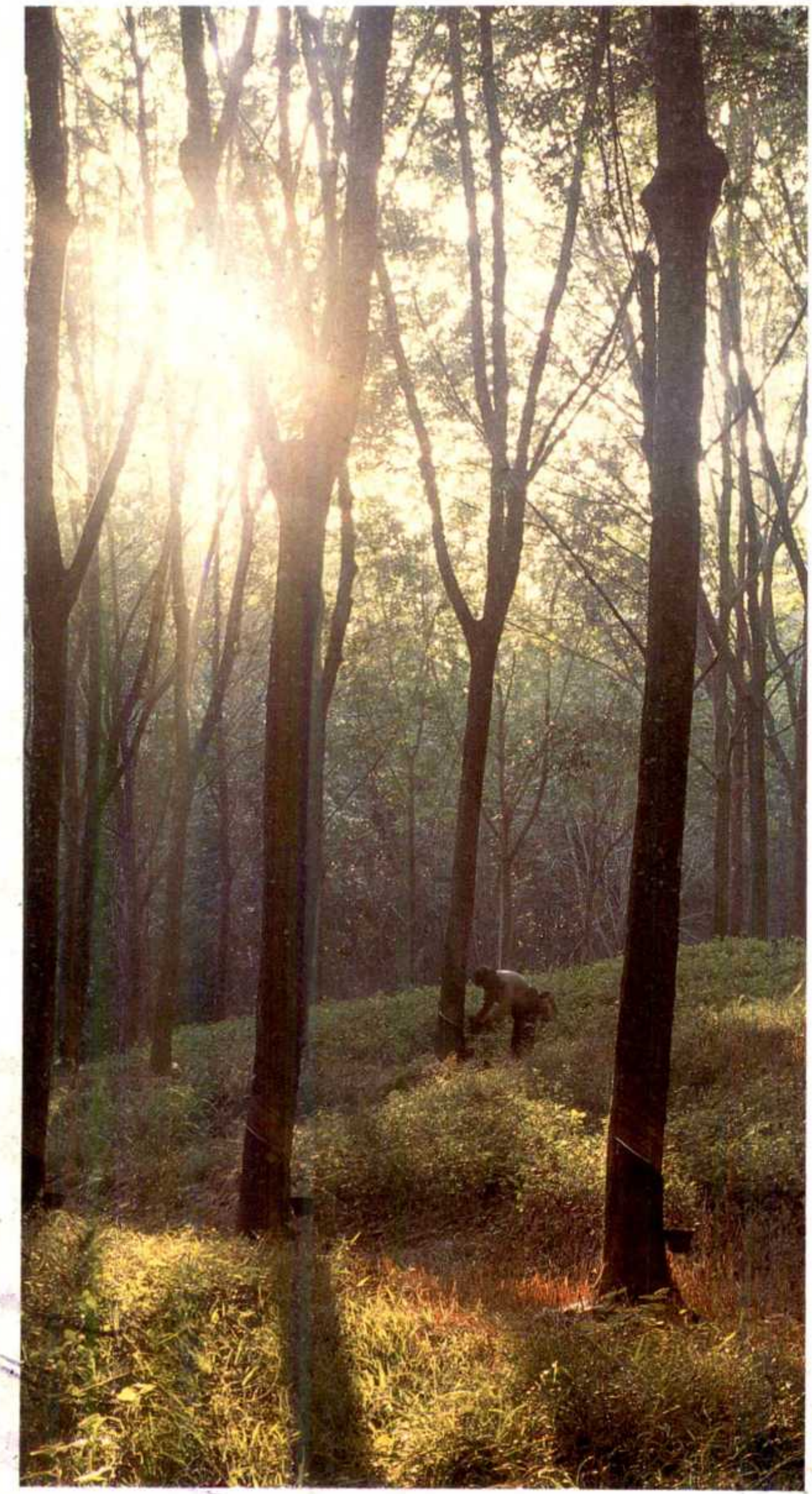

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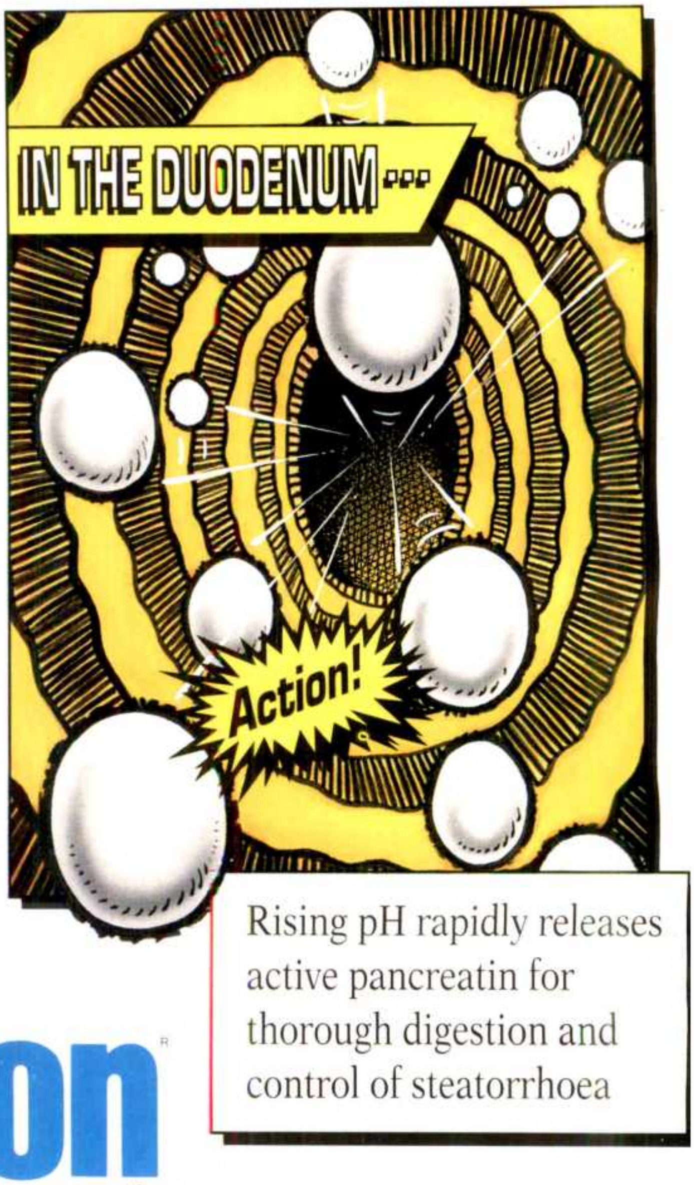
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References

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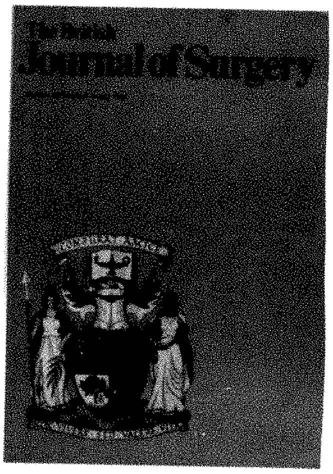

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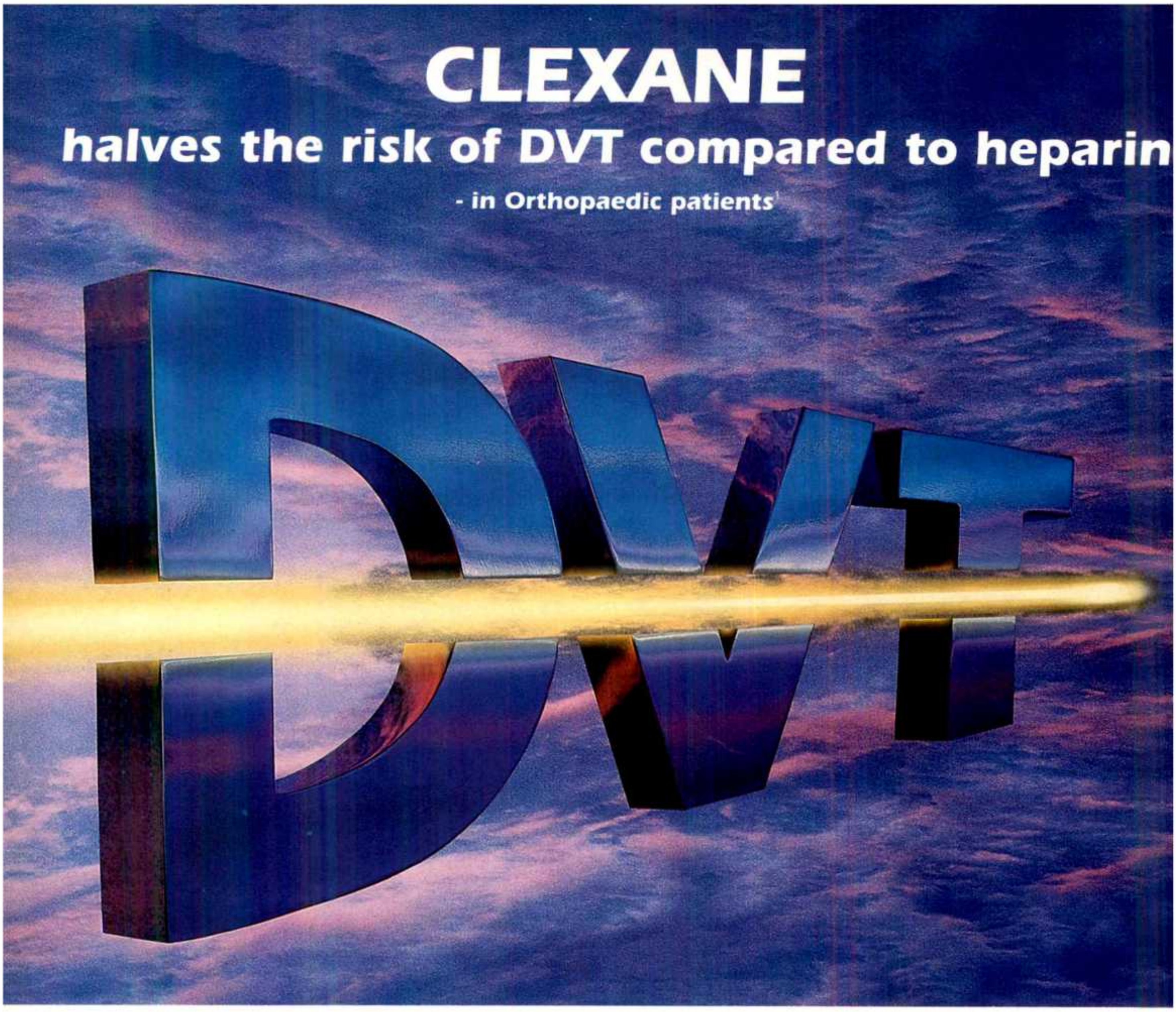
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Br. J. Surg. 1991, Vol. 78, November, 1281–1282

Immunotherapy for cancer

The last decade has witnessed a phenomenal increase in technological developments in the biological sciences. These include such procedures as somatic cell hybridization for the production of murine and human monoclonal antibodies, recombinant technology for the production of growth factors which were otherwise unobtainable in large quantities by cell culture techniques, and retroviral gene transfer for the genetic modification of cells[1]. These and other procedures have facilitated the development of contemporary immunotherapy for certain types of malignant disease.

For the classical immunologist the generation of endogenous tumour-specific immune responses was unthinkable in the absence of any convincing evidence for the existence of tumour-specific antigens. However, there is now overwhelming evidence for the presence of such antigens on at least one human tumour, malignant melanoma, against which autologous tumour-specific cytotoxic T lymphocytes have been identified in most patients[2]. These specific tumour-infiltrating lymphocytes (TIL) lyse the patient's own tumour cells in a major histocompatibility complex (MHC)-restricted fashion and do so with approximately 100 times the efficacy of peripheral blood lymphocytes (lymphokine-activated killer (LAK) cells) activated non-specifically with the T cell growth factor interleukin 2 (IL-2). Furthermore, when these activated TIL cells are expanded with IL-2 and transferred back adoptively into the patient, they specifically 'home' into tumour sites[3] and, in combination with IL-2 infusion, have been reported to cause tumour regression in 50 per cent of patients so treated[4]. Current experiments are in progress to modify these TIL cells genetically, arming them with activated genes for cytotoxic cytokines, such as tumour necrosis factor (TNF), so that when they home into secondary tumour sites, they release the cytokines and bring about oncolysis[5].

Adoptive cellular immunotherapy with *in vitro* activated LAK or TIL cells is, at present, highly labour-intensive and requires skills which are not universally available. Whether or not treatment with genetically modified TIL cells will be successful remains to be seen, but the concept of tailoring individual therapy for particular patients is an attractive one. However, in practical terms it is likely that immunotherapy will only really be accepted if it can be taken 'off the shelf' and administered without the necessity for the complexities and potential hazards of *ex vivo* lymphocyte manipulation.

Nevertheless, current results provide a forcible argument that for advanced malignant melanoma and hypernephroma IL-2-based treatments, perhaps in combination with recombinant interferons, provide the highest tumour response rates and are associated with prolonged survival[6]. The cost of such treatments, both financial and in terms of toxicity, has led some to question their application. However, many of the patients suffering from these otherwise untreatable diseases are young, and it seems quite unreasonable that they should be refused the opportunity of a 25 per cent chance of responding to combination therapy with IL-2 simply on the basis of cost, which is little more than that for a course of one of the newer antibiotic combinations.

Can these approaches be exploited for the treatment of other tumours? As yet the generation of tumour-specific cytotoxic T lymphocytes has not been convincingly demonstrated for the majority of common tumours. Similarly, attempts to use the patient as his or her own 'test-tube' for the generation of cytotoxic cells by administering IL-2 alone seem to be effective in only 15–25 per cent of those patients with susceptible tumours. Considerable evidence exists to suggest that this is not simply due to the failure of such tumours to express tumour-specific antigens, together with HLA-antigens, but also because of the elaboration of potently suppressive molecules by the tumours themselves, thus subverting the endogenous anti-tumour response[7,8]. Once the identity of these moieties has been ascertained, other strategies might be invoked to evade their influence. This may be of importance even in the absence of defined tumour-specific antigens since the expression of oncogene-encoded proteins may also serve both as sensitizing molecules and target structures for the generation of specific cytotoxic lymphocytes against tumours such as colorectal

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cancer. This concept is becoming a major focus of intensive research by tumour immunologists[9].

It must not be forgotten that recombinant technology has also provided us with reagents whose beneficial therapeutic effects cannot be entirely explained on an immunological basis. For example, the recent description of response rates in excess of 50 per cent in patients with advanced colorectal cancer treated with a combination of 5-fluorouracil and recombinant α_2-interferon[10] represents an important advance which is under detailed study in phase II/III trials. Similarly, cytotoxic drugs may potentiate the biological effects of recombinant cytokines and result in clinically advantageous therapeutic responses[11]. In view of recent reports, these findings may have important implications for the development of adjuvant therapy for colorectal cancer[12]. This is entirely in keeping with the concept that biological therapies are most effective in the presence of minimal residual disease.

Enthusiasm for cancer immunotherapy has waxed and waned over the past half century but has become invigorated by the 'new biology'. The present renaissance of immunotherapy promises to be durable simply because, at long last, it appears to be effective for certain types of malignancy. The challenge is to expand the frequency and the repertoire of responsive tumours.

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1. Guillou PJ. Potential impact of immunobiotechnology on cancer therapy. *Br J Surg* 1987; **74**: 705–10.
2. Muul LM, Spiess PJ, Director EP, Rosenberg SA. Identification of specific cytolytic immune responses against autologous tumour in humans bearing malignant melanoma. *J Immunol* 1987; **138**: 989–95.
3. Fisher B, Packard BS, Read EJ *et al.* Tumour localisation of adoptively transferred indium-111 labelled tumour infiltrating lymphocytes in patients with metastatic melanoma. *J Clin Oncol* 1989; **7**: 250–61.
4. Rosenberg SA, Packard BS, Aebersold PM *et al.* Use of tumour-infiltrating lymphocytes and interleukin-2 in the immunotherapy of patients with metastatic melanoma: a preliminary report. *N Engl J Med* 1988; **319**: 1676–80.
5. Rosenberg SA, Aebersold P, Cornetta K *et al.* Gene transfer into humans – immunotherapy of patients with advanced melanoma using tumor-infiltrating lymphocytes modified by retroviral gene transduction. *N Engl J Med* 1990; **323**: 570–8.
6. Rosenberg SA, Lotze MR, Yang JC *et al.* Combination therapy with interleukin-2 and alpha-interferon for the treatment of patients with advanced cancer. *J Clin Oncol* 1989; **7**: 1863–74.
7. Guillou PJ, Sedman PC, Ramsden CW. Inhibition of lymphokine-activated killer cell generation by cultured tumour cell lines *in vitro. Cancer Immunol Immunother* 1989; **28**: 43–53.
8. Guillou PJ, Ramsden CW, Somers SS, Sedman PC. Suppression of the generation of lymphokine-activated killer (LAK) cells by serum-free supernatants of *in vitro* maintained tumour cell lines. *Br J Cancer* 1989; **59**: 515–21.
9. Bodmer W. T-cell immune responses to cancer – a new look. *Hum Immunol* 1991; **30**: 259–61.
10. Wadler S, Wiernik PH. Clinical update on the role of fluorouracil and recombinant interferon alpha 2a in the treatment of colorectal carcinoma. *Semin Oncol* 1990; **17**(Suppl); 16–21.
11. Onodera H, Somers S, Guillou PJ. Paradoxical effects of 5-FU/folinic acid on LAK cell induction in patients with colorectal cancer. *Br J Cancer* 1990; **62**: 1042–6.
12. Moertel CG, Fleming TR, Macdonald JS *et al.* Levamisole and fluorouracil for surgical adjuvant therapy of colon carcinoma. *N Engl J Med* 1990; **322**: 352–8.

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Use of the appendix in reconstructive surgery: a case against incidental appendicectomy

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Ignored for years, the appendix is once again being promoted as having useful surgical potential, notably in the management of incontinence. Incidental and prophylactic appendicectomy with their established complications become less easy to justify as the incidence of appendicitis declines. The role of the appendix in reconstructive surgery is reviewed, with particular reference to urinary reconstruction and to the treatment of chronically constipated or faecally incontinent children by use of the antegrade continence enema.

The appendix has played conflicting roles in surgical practice over the years, having been ignored, conserved, variously utilized or prophylactically excised. Recently the conservationists have once again promoted this vestigial organ as having surgical potential, particularly in the field of incontinence management.

The vermiform appendix is found only in humans, certain anthropoid apes and the wombat[1]. It may be considered a specialized structure, rather than being degenerate and vestigial, on the basis of its histological differentiation and rich blood supply. Its collections of lymphoid tissue have led to the suggestion that the appendix is homologous to the bursa of Fabricius in birds, although this is not supported by experimental evidence[2]. Many herbivorous mammals possess a wide caecal diverticulum in which bacterial degradation of cellulose occurs, but this lacks the lymphoid tissue characteristic of the appendix[1]. Although the exact role of the appendix is not known, it is regarded as serving no useful function but having the potential for mischief. Life-table analysis indicates a risk over a period of 40 years of 0·0431 and 0·0369 for developing acute appendicitis in men and women respectively[3,4]. The incidence is even higher in younger patients and a mortality rate of one in 800 is reported[3].

Incidental appendicectomy

Because of the risk of appendicitis, the appendix has been removed incidentally at abdominal operations and prophylactically in servicemen embarking on extended expeditions such as the British Antarctic Survey and space missions. When Lawson Tait's first operation was performed 111 years ago[5], appendicitis was a rare disease. It rapidly became more common but, if the postwar trend continues, it is about to become rare again. Although there might have been a case for prophylactic appendicectomy when appendicitis was common, that justification vanishes if the condition is increasingly unlikely to occur.

Incidental appendicectomy is widely discussed in relation to cholecystectomy[6–11], inguinal herniorrhaphy[12], vaginal surgery[13–15], caesarean section[16,17], exploration of ectopic pregnancy[18,19], correction of malrotation, and in patients with Crohn's disease[20]. The influence of age on the outcome of incidental appendicectomy has also been discussed[21]. Complications of the operation are widely reported, such as increased incidence of wound infection (5–25 per cent)[22–25], priapism[26], and recurrent inguinal hernia[27].

Closed techniques have been developed in an effort to reduce some of these complications. Inversion appendicectomy has been described in children, particularly in North America; other than postoperative intussusception, it has been free from complication[28–30].

Retrospective reports suggest an increased risk of colonic, breast and ovarian cancers, and lymphoma in appendicectomized individuals, but a prospective study using a control group of oral surgery and orthopaedic patients failed to confirm this[31].

The appendix in reconstructive surgery

A common argument used against the practice of incidental appendicectomy is the potential value of the appendix in the field of surgical reconstruction. The appendix has been used in biliary[32,33] and tubal[34] surgery, but the techniques have not gained widespread acceptance. Its use in reconstructive surgery has instead been mainly in the field of urology.

Early this century, connection of the ureters to the appendix[35,36] was thought to confer an advantage over the distal colon as a diversionary route resulting in fewer urinary infections[37], but both the operative mortality rate and the number of perioperative complications were unacceptably high. The appendix was then used as a natural conduit after ureteric reimplantation into an artificial bladder formed from the ileocaecal region[38]. This, too, was prone to postoperative complications, and the use of the appendix in urological reconstruction lapsed.

Recent advances

In 1980 the situation changed. In the search for a continent catheterizable cystostomy, Mitrofanoff[39] reported the use of the appendix, isolated on its vascular pedicle, implanted into the bladder in a non-refluxing manner. The appendix was tunnelled submucosally into the bladder and brought out on to the abdominal wall to a funnel of skin, facilitating catheterization through a continent stoma.

This principle is now widely practised in urological surgery both on the native bladder and on the enteric pouches commonly used in urinary undiversion[40,41]. It has proved to be particularly successful in wheelchair-bound neuropathic patients and in patients for whom urethral catheterization is not acceptable. Mitrofanoff's initial series of operations on 16 children has been extended by others[41–47] to establish the procedure as a commonly used technique in paediatric urology.

In Mitrofanoff's original series, the only failures were due arguably to case selection; children with high-pressure neuropathic bladders developed hydronephrosis and for them simultaneous augmentation should have been performed. In a

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series of 30 reconstructions over a 6-year period reported by Snyder[48], continence (defined as being dry between catheterizations at 4-h intervals) was achieved in all but one case, in which the appendix was said to be over-dissected and sloughed. A total of 16 patients reported by Woodhouse *et al.*[43] underwent the Mitrofanoff procedure during urinary reconstruction, the appendix being used in five cases. All the patients were continent, but in two the stoma strictured, requiring minor revision. The Mitrofanoff procedure has also played a role in post-traumatic urethral reconstruction, with the appendix being successfully used in a patient who suffered a disrupted urethra following pelvic trauma[48]. The place of the appendix as a continent catheterizable stoma in urological reconstruction has been established in a successful technique that has stood the test of time.

In a comparison with the Koch pouch, Cumming *et al.*[49] recorded successes (in terms of complete continence) in six of seven patients undergoing the Mitrofanoff procedure, at the price of three revisions in two cases. This was in contrast to successes in two of six cases with the Koch pouch, needing ten revisions in four to make a further two patients continent. There have been attempts at modification of Mitrofanoff's procedure using partial invagination of the appendix into the caecum, together with caecoplication around the mid-third of the appendix[47]. The aim is to obtain appendiceal continence without the need for appendiceal isolation. However, this has limited use and no long-term follow-up information is available.

Antegrade continence enema

In 1990, Malone *et al.* described an adaptation of the Mitrofanoff procedure for the treatment of the chronically constipated or faecally incontinent child, the antegrade continence enema (ACE)[50]. This procedure combined the principles of Mitrofanoff with total colonic irrigation[51,52] to facilitate the antegrade administration of enemas, producing total colonic emptying and thus relieving chronic constipation and incontinence.

The ACE procedure is accomplished by isolating the appendix from the caecum on its vascular pedicle. The appendix is reversed and its distal end amputated before reimplantation in a non-refluxing fashion into the caecum. Its proximal end is brought out through the abdominal wall as a continent stoma. A continent catheterizable channel is now available for the intermittent administration of antegrade enemas while the patient sits on the toilet.

The procedure has been performed in 13 patients whose ages ranged from 3 to 18 years. Three patients suffered from intractable chronic idiopathic constipation, and the remaining ten from a combination of constipation and faecal incontinence secondary to a variety of causes: myelomeningocele (four), anorectal malformation (four), sacral agenesis (one) and spinal injury (one). Follow-up ranged from 1 to 20 months. The time taken to achieve colonic emptying following administration of the enema varied from 20 to 30 min. Two patients experienced minor leakage of rectal fluid, but the other 11 remained completely clean between enemas given at an interval that varied from 48 to 72 h. Most patients used a phosphate enema, with some requiring a subsequent saline washout of varying volume. The procedure successfully achieved colonic emptying in each case, but one patient developed severe stomal stenosis, requiring repeated dilatations, and is now awaiting a revision procedure. No other complications were encountered.

ACE has revolutionized bowel care in these cases and is of particular benefit to wheelchair-bound patients, who can perform the procedure by themselves and thus become completely independent.

Comment

With newer diagnostic techniques such as ultrasonography[53] and laparoscopy[54,55], the incidence of negative laparotomy in pursuit of the diagnosis of appendicitis should fall and the appendix should therefore increasingly be preserved. There are clearly defined groups in which the appendix should be conserved expectantly, e.g. patients with spina bifida, high anorectal malformations, cloacal exstrophy and Hirschsprung's disease, who are likely to suffer long-term problems of bowel emptying and who may become candidates for the ACE procedure. Children with exstrophic or neuropathic bladders may benefit from the Mitrofanoff procedure to aid intermittent self-catheterization.

There are less well defined groups in which the presence of a normal appendix is fortuitous, for instance patients with spinal injuries and tumours, and those with chronic idiopathic constipation. To perform an incidental appendicectomy may be convenient, expedient and relatively complication-free, but recent developments demonstrate the value of the appendix in the field of reconstructive urology and in the management of faecal incontinence. The authors would suggest that the procedure of incidental appendicectomy should be abandoned to preserve the appendix for future use should the need arise.

References

1. *Bailey and Love's Short Practice of Surgery*. 18th ed. London: H. K. Lewis, 1981: 1055.
2. *Gray's Anatomy*. 35th ed. Harlow: Longman, 1973: 1288.
3. Cuschieri A. The small intestine and vermiform appendix. In: Cuschieri A, Giles GR, Moossa AR, eds. *Essential Surgical Practice*. Bristol: John Wright, 1988: 1162.
4. Sugimoto T, Edwards O. Incidence and costs of incidental appendectomy as a preventative measure. *Am J Public Health* 1987; **77**: 471–5.
5. *Bailey and Love's Short Practice of Surgery*. 18th ed. London: H. K. Lewis, 1981: 1067.
6. Voitk AJ, Lowry JB. Is incidental appendectomy a safe practice? *Can J Surg* 1988; **31**: 448–51.
7. Cooper G, Taylor WS, Golstein PJ. Incidental appendectomy: the controversy. *Md Med J* 1987; **36**: 833–6.
8. Moore FD. Incidental appendectomy. *Am J Public Health* 1987; **77**: 1015–16.
9. Tranmer BI, Graham AM, Sterns EE. Incidental appendectomy? Yes. *Can J Surg* 1981; **24**: 191–2.
10. Ashbury GF. Incidental appendectomy. *Am Surg* 1974; **40**: 518–20.
11. Silvert MA, Meares EM. Rationale of incidental appendectomy. *Urology* 1976; **7**: 129–34.
12. Shumake LB. Right inguinal herniorrhaphy and incidental appendectomy. *Am Surg* 1971; **37**: 650–2.
13. Reiner IJ. Incidental appendectomy at the time of vaginal surgery. *Tex Med* 1980; **76**: 46–50.
14. Massoudnia N. Incidental appendectomy in vaginal surgery. *Int Surg* 1975; **60**: 89–90.
15. McGowan L. Incidental appendectomy during vaginal surgery. *Am J Obstet Gynecol* 1966; **95**: 588.
16. Tungphaisal S, Pinjaroen S, Chandeying V *et al.* Incidental appendectomy at cesarian section: a prospective study. *J Med Assoc Thai* 1989; **72**: 633–7.
17. Parsons AK, Sauer MV, Parsons MV *et al.* Appendectomy at cesarian section: a prospective study. *Obstet Gynecol* 1986; **68**: 479–82.
18. Onuigbo WI. Elective appendectomy at salpingectomy for ectopic pregnancy: is it desirable? *Obstet Gynecol* 1977; **49**: 435–7.
19. Cromartie AD, Kovalcik PJ. Incidental appendectomy at the time of surgery for ectopic pregnancy. *Am J Surg* 1980; **139**: 244–6.
20. Simonowitz DA, Rusch VW, Stevenson JK. Natural history of incidental appendectomy in patients with Crohn's disease who required subsequent bowel resection. *Am J Surg* 1982; **143**: 171–3.
21. Nockerts SR, Detmer DE, Fryback DG. Incidental appendectomy in the elderly? No. *Surgery* 1980; **88**: 301–6.
22. Andrew NH, Roty AR. Incidental appendectomy with cholecystectomy: is the increased risk justified? *Am Surg* 1987; **53**: 553–7.
23. Morris DM, Coker DD, Coleman JJ *et al.* Effect of incidental appendectomy on the development of wound infection in patients undergoing staging laparotomy for Hodgkin's disease. *Am J Surg* 1987; **153**: 226–9.

24. Ikard RW. Prospective analysis of the effect of incidental appendectomy on infection rate after cholecystectomy. *South Med J* 1987; **80**: 292–5.
25. O'Malley VP, Finch DR, Powley PH. Wound sepsis after cholecystectomy: influence of incidental appendicectomy. *J Clin Gastroenterol* 1986; **8**: 435–7.
26. Gue S. Priapism: an unusual sequela of appendicectomy; case report with review of the literature. *Aust NZ J Surg* 1974; **44**: 60–2.
27. Gue S. Development of right inguinal hernia following appendicectomy: a 10 year review of cases. *Br J Surg* 1972; **59**: 352–3.
28. Bishop HC, Filston HC. An inversion–ligation technique for incidental appendectomy. *J Pediatr Surg* 1973; **8**: 889–92.
29. Lilly JR, Randolph JG. On the inversion technique of incidental appendectomy. *J Pediatr Surg* 1973; **8**: 887.
30. Lilly JR, Randolph JG. Total inversion of the appendix: experience with incidental appendectomy in children. *J Pediatr Surg* 1968; **3**: 357–63.
31. Lee Y. Appendectomy, tonsillectomy and neoplasia. *J Surg Oncol* 1975; **7**: 237–41.
32. Grosfeld JL, Weinberger M, Clatworthy HW. Vascularized appendiceal transplants in biliary and urinary tract replacement. *J Pediatr Surg* 1971; **6**: 630–8.
33. Grosfeld JL, Clatworthy HW. Common bile duct substitution using vascularized appendiceal transplants. *Surg Forum* 1970; **21**: 389–91.
34. Halelmira S, Thumaporn M, Buranavithayanon H. An effective appendiceal uterine transplantation: a follow up study. *Int Study* 1968; **50**: 469–73.
35. Babcock W. A note as to the recognition of the ureter: report of a case of anastomosis of the ureter into the appendix. *Surg Gynecol Obstet* 1914; **18**: 119–20.
36. Eaton GL. Transplantation of right ureter into appendix. *Am J Urol* 1910; **6**: 230–2.
37. Thorne ID, Resnick MI. The use of bowel in urological surgery. *Urol Clin North Am* 1986; **13**: 179–91.
38. Hinman F, Weyrauch HM. A critical study of the different principles of surgery which have been used in ureterointestinal implantation. *Trans Am Assoc Genitourin Surg* 1936; **29**: 15–156.
39. Mitrofanoff P. Cystomie continente trans-appendiculaire dans le traitment des vessies neurologiques. *Chir Pediatr* 1980; **21**: 297–305.
40. Mitchell ME. Use of bowel in undiversion. *Urol Clin North Am* 1986; **13**: 349–58.
41. Weingarten JL, Cromie WJ. The Mitrofanoff principle: an alternative form of continent urinary diversion. *J Urol* 1988; **140**: 1529–31.
42. Duckett JW, Snyder HM. Use of the Mitrofanoff principle in urinary reconstruction. *Urol Clin North Am* 1986; **13**: 271–4.
43. Woodhouse CR, Malone PR, Cumming J, Reilly TM. The Mitrofanoff principle for continent urinary diverson. *Br J Urol* 1989; **63**: 53–7.
44. Longaker MT, Harrison MR, Langer JC *et al.* Appendicovesicostomy: a new technique for bladder diversion during the reconstruction of cloacal exstrophy. *J Pediatr Surg* 1989; **24**: 639–40.
45. Issa MM, Oesterling JE, Canning DA, Jeffs RD. A new technique of using the *in situ* appendix as a catheterisable stoma in continent urinary reservoirs. *J Urol* 1989; **141**: 1385–7.
46. Montfort G, Guys JM, Lacombe GM. Appendicovesicostomy: an alternative urinary diversion in the child. *Eur Urol* 1984; **10**: 361–3.
47. Mollard P. Transappendicular continent cystostomy: critical study apropos of 30 cases. *Ann Surg* 1988; **208**: 337–44.
48. Snyder HM. Surgical management of urinary incontinence in children. *Surg Clin North Am* 1988; **68**: 909–43.
49. Cumming J, Worth PHL, Woodhouse CR. The choice of suprapubic continent catheterisable urinary stoma. *Br J Urol* 1987; **60**: 227–30.
50. Malone PS, Ransley PG, Keily EM. Preliminary report: the antegrade continence enema. *Lancet* 1990; **336**: 1217–18.
51. Hewitt J, Rigby J, Reeve J, Cox AG. Whole gut irrigation in preparation for large bowel surgery. *Lancet* 1973; **ii**: 337–40.
52. Radcliffe AG, Dudley HAF. Intraoperative antegrade irrigation of the large intestine. *Surg Gynecol Obstet* 1983; **156**: 721–3.
53. Deutsch A, Leopold GR. Ultrasonic demonstration of the inflamed appendix. *Radiology* 1981; **140**: 163.
54. Leape LL, Ramenofsky ML. Laparoscopy for questionable appendicitis: can it reduce the negative appendectomy rate? *Ann Surg* 1980; **191**: 410.
55. Deutsch AA, Zelikovsky A. Laparoscopy in the prevention of unnecessary appendectomies: a prospective study. *Br J Surg* 1982; **69**: 336.

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Peptide growth factors and wound healing

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Growth factors and cytokines are important signal transducers in wound microenvironments. Experimental data are accumulating rapidly which demonstrate their ability to influence populations of polymorphs and macrophages to migrate to the wound, subsequently to be replaced by synthetic cells which produce collagen and matrix; these events are controlled sequentially at cell receptor level by a variety of locally delivered (paracrine and autocrine) peptides. Preliminary results from clinical trials using recombinant human growth factors to improve cutaneous healing are encouraging. Current research aims to produce growth preparations which can be applied to a wound to accelerate healing.

Wound healing is a complex interaction between components of the extracellular matrix and migratory cells from the vascular compartment. Studies of healing wounds demonstrate a characteristic sequence of cellular infiltration: neutrophils appear during the first 48 h, macrophage numbers increase at 2 days, and fibroblasts begin to appear in greater numbers from about 3 days. Fibroblasts synthesize the collagen and matrix that form the developing granulation tissue. The arrival of cells at a wound site, their multiplication and synthetic activity are mediated by a variety of recently identified cytokines[1]. Growth factors are implicated as messengers in wound healing, and recombinant DNA technology allows the production of these peptides in pure form and in pharmacological quantities[2]. Conservation of growth factor peptide sequences between species suggests evolutionary preservation for fundamental physiological reasons, and supports an essential role for these substances as biological regulators of cell division and differentiation. A number of peptide growth factors have been shown to affect the parameters with which healing is assessed in simple *in vivo* models[3–7].

Tissue repair is initiated by release of growth factor peptides, such as transforming growth factor beta (TGF-β), platelet-derived growth factor (PDGF) and epidermal growth factor (EGF) from platelet α-granules[8–11]. These peptides are chemotactic for both macrophages and fibroblasts. Cells move up a concentration gradient towards the centre of the wound and, on reaching the wound centre, are stimulated to divide[12]. Macrophages are now seen as having a critical role in the control of subsequent events. They secrete a large number of peptides implicated in wound healing mechanisms, including TGF-β, TGF-α, PDGF, basic fibroblast growth factor (bFGF) and tumour necrosis factor (TNF)[13–16]. The ultimate aim in a healing wound is production of granulation tissue, and eventually replacement of this with mature scar tissue; it is suggested that peptide growth factors function in a manner analogous to a cascade in order to produce these effects[17]. Individual growth factors may be selective in the events they influence: both PDGF and TGF-β promote fibroblast proliferation *in vitro*, while TGF-β promotes fibroblast differentiation and the assumption of a phenotype associated with the production of collagen and matrix. PDGF on the other hand stimulates secretion of collagenase and fibronectin[18,19].

The composition of the extracellular matrix may profoundly affect the action of growth factors. Cellular adhesion to matrix and associated protein molecules determines cellular phenotype and receptor expression. In addition, the matrix affects the solubility of growth factor peptides (bFGF and PDGF) and hence their ability to transduce signals for replication or protein (collagen) synthesis[20]. Matrix may act as a reservoir for growth factor which can be liberated by the appropriate signal, e.g. tissue injury[21].

The clinical use of growth factors to stimulate wound healing is currently under intense investigation[22]. The greatest potential for exploitation of growth factors will be in areas where the morbidity from wound failure is significant, such as in the gastrointestinal tract, or in situations where wound failure is more likely to be because of some systemic impairment of the healing process. In experimental animals, growth factors are capable of reversing deficient wound healing caused by diabetes, glucocorticoids, irradiation or chemotherapy[23–26].

In vitro studies

Several *in vitro* methods have been used to investigate the effects of growth factors on the individual cellular elements involved in connective tissue formation. Extrapolation to the situation *in vivo*, however, may not be appropriate because of the complex molecular and cellular interactions within a wound. Using simple assays, TGF-β and PDGF can be shown to be chemotactic for monocytes at physiological concentrations[27,28]. FGF, TGF-β and PDGF are all chemotactic for fibroblasts[29–31].

Most peptide growth factors are mitogenic for fibroblasts grown in culture. Cell culture studies have investigated the effects of growth factors on collagen and matrix protein synthesis. TGF-β stimulates the transcription of the messenger RNA (mRNA) for procollagen and matrix proteins and increases the production of these proteins by a number of cell lines *in vitro*[32–38]. TGF-β increases production of a metalloproteinase collagenase inhibitor *in vitro*[39]. EGF (2–5 ng/ml) added to human skin fibroblasts in culture increases the synthesis of non-collagenous proteins and hyaluronic acid[40]. Basic FGF and PDGF increase collagenase production, which is essential for the restructuring of collagen for cellular migration[29]. Basic FGF is mitogenic and chemotactic for endothelial cells *in vitro*, suggesting a role in new vessel formation (angiogenesis) and granulation tissue formation[41]. The contraction of collagen lattices by fibroblasts *in vitro* may partially resemble the phenomenon of wound contraction, and TGF-β can be shown to promote this energy-dependent process *in vitro*[42].

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Experimental animal studies

Implantation of a subcutaneous wound chamber represents an artificial form of injury defining a space in which a number of specific parameters (e.g. cellularity, collagen content, DNA content) can be used to assess the healing process. Wound fluid from such chambers contains EGF/TGF-α, TGF-β and PDGF-like activity[43–45]. When small numbers of monocytes removed from wound chambers are disrupted, their mRNA isolated, reverse-transcribed, and amplified using the polymerase chain reaction with primers for a number of known peptides including growth factors, activated monocytes can be shown to contain transcript copies of the mRNA species of TGF-α, TGF-β and PDGF[14]. Implantation of a polyvinyl alcohol sponge also defines a wound space, but the sponge provokes an inflammatory reaction which accelerates accumulation of cellular elements[46–49]. In this model, single doses of EGF do not have any effect on granulation tissue formation; however, EGF injected daily (dose range 0·2–10 mg) has a dose-dependent effect by increasing granulation tissue formation. Glycosaminoglycan, collagen synthesis and granulation tissue production are increased by the implantation of pellets containing EGF in the sponge which is released slowly over a period of days. Exogenous TGF-β as a single injection increases the deposition of collagen in a polyvinyl alcohol sponge[23].

The cellularity of granulation tissue produced in the interstices of a cylindrical polytetrafluoroethylene chamber can be increased two to six times by a single injection into the chamber lumen of low concentrations (100–400 ng) of PDGF, TGF-β and bFGF in a collagen gel. The half-life of iodinated peptide within a gel is approximately 20 h and the most potent peptide is TGF-β[50]. In a small wire-mesh chamber implanted subcutaneously (the Hunt-Schilling chamber), an injection of 50 ng PDGF increases collagen synthesis by 73 per cent in comparison to control chambers, for a period of 2 weeks[51].

Angiogenesis is a critical part of the formation of granulation tissue. TGF-β, TNF and bFGF in simple *in vivo* angiogenic assays are all potently angiogenic; however, of these only FGF is chemotactic or mitogenic for endothelial cells *in vitro*, suggesting an indirect action by the other peptides[52]. Using an assay which measures the time taken for a radioactive label to be removed from a subcutaneous sponge containing granulation tissue, TGF-α injected at a dose of 3 μg daily appears to increase capillary angiogenesis[53].

A number of investigators have applied growth factor to an experimental wound in animals and observed the effect on healing. A widely used model of healing by first intention involves the construction of paired linear cutaneous incisions; one is treated and the other acts as a control wound. Healing is assessed by measurement of the breaking strength. EGF applied to the open wound in single doses at the time of surgery does not affect wound strength. However, when EGF is injected into the wound daily or incorporated (10 μg) in multilamellar liposomes (to prolong release), an increase in tensile strength of up to 200 per cent occurs in skin wounds of rats at 7 and 14 days[54]. With a similar model, applications of TGF-β or PDGF in saline fail to produce any significant effect on breaking strength. A single application of TGF-β (2 μg) in a collagen suspension increases breaking strength by 220 per cent at 7 days after wounding[55]. The positive effects are apparent between 7 and 14 days and are equivalent to an acceleration of the healing process of about 3 days. A single application of 20 μg PDGF in a collagen suspension increases the strength of wounds by 200 per cent at 7 days and the positive effects of PDGF are still apparent at 40 days[56]. Some evidence has been provided that use of a collagen suspension delays release of peptide by a few hours in experiments *in vitro*. With both TGF-β and PDGF a dose response curve is apparent. Wounds treated with both peptides demonstrate an augmented cellular infiltrate during the early days of healing and, in the case of PDGF, increased staining of tissue sections with a monoclonal antibody to procollagen type I[56]. Local TNF increases wound disruption strength by 23–49 per cent in incisional wounds in mice in a narrow dose range (50–500 ng). Outside this range its effect on wound strength appears to be inhibitory and is associated with a dense inflammatory infiltrate[57]. When infiltrated into healing incisional wounds on the third day after wounding, 500 ng recombinant bFGF increases breaking loads of treated wounds by 39 per cent[58]. When applied to the open wound before closure, the effect of bFGF (50 μg) is deleterious, but when release is delayed by incorporation of bFGF into red blood cell ghosts, a 50 per cent increase in breaking strength is seen at 7 days[59].

A number of attempts have been made to assess histomorphometrically the effects of peptide growth factors on the deposition of the various elements of healing wounds. The local application of TGF-β or PDGF in an albumin or cellulose gel can increase connective tissue formation in open rectangular porcine epidermal wounds[60–62]. Attempts have been made to see whether the effects of growth factors can be improved by applying them in combination. Of six peptides applied topically in 3 per cent methyl cellulose gel to partial-thickness skin wounds in pigs, only a combination of PDGF and insulin-like growth factor (IGF) in a 2:1 mixture increases collagen deposition (fourfold increase) and dermal thickness (twofold increase) by as much as a single application of 1500 ng TGF-β[62]. In guinea-pig dermal wounds healing by secondary intent, 5 μg TGF-β type II, delivered in a sponge composed of collagen and heparin, increases morphometrically apparent connective tissue formation at day 8 and significantly increases wound strength[63]. Cutaneous healing can be considered to have an epithelial and a connective tissue component. Locally-applied human recombinant EGF increases healing of split-thickness epidermal wounds and partial-thickness skin wounds in pigs; histological analysis demonstrates increased cellularity, epithelialization and thickness of granulation tissue[64,65]. TGF-α, applied in antibiotic cream at a dose of 0·1 μg/ml, also increases epidermal regeneration in open porcine skin wounds[66].

A major difficulty in interpreting the mode of action of local applications of peptide *in vivo* and understanding the processes involved is that many of the effects may be mediated through the paracrine/autocrine production of further peptides. *In situ* hybridization allows examination of the genes being transcribed within the complex architecture of a healing wound. Using an excisional skin model in the pig, increased staining for collagen and matrix protein mRNA is apparent after treatment with exogenous TGF-β[61]. Staining for TGF-β mRNA is also increased, which suggests positive feedback regulation. This observation provides an explanation for the mechanism of action of growth factor applied at the time of wounding, where the half-life of exogenous growth factor is normally only a few hours. An initial high dose of TGF-β stimulates a mononuclear cell infiltrate and the autocrine/paracrine production of further TGF-β. This is supported by *in vitro* studies, with TGF-β stimulating the production of further TGF-β by both normal and transformed cells[67].

Impaired healing

The greatest therapeutic benefit of growth factors may occur when impaired healing results in increased morbidity and mortality rates. In animals, deficient wound healing can be successfully ameliorated by growth factors. Wound healing impaired by corticosteroids is well documented. Animals may be considered in two groups: steroid-sensitive and steroid-resistant. In the former, treatment with steroids causes profound monocytopenia, which prevents migration of a critical cell involved in the wound healing cascade[68]. Many investigators have documented the negative *in vitro* effects of steroid treatment on fibroblast function, such as impaired DNA, procollagen and matrix protein synthesis[69–72]. The rat is steroid-sensitive, and a single local application of 2 μg TGF-β in a collagen suspension reverses a 50 per cent decrease in wound strength at 7 days resulting from glucocorticoid treatment. PDGF in the same model fails to reverse the wound healing deficit[24]. The authors suggest that this is because the mode of action of PDGF *in vivo* is by recruitment of monocytes to a healing wound, and subsequent production of TGF-β is from those cells. *In vitro* macrophages can be shown to produce TGF-β in response to PDGF. In a pig excisional wound model, steroid-treated animals had local applications of exogenous TGF-β and, together with an increase in matrix protein and procollagen mRNA staining, increased staining of TGF-β mRNA was apparent[73]. Many of the effects of TGF-β on cells *in vitro* are the converse of steroid treatment, suggesting that the effects of exogenous peptide are direct, although mediated by the autocrine/paracrine production of further growth factor. In cultured fibroblasts EGF does not restore dexamethasone-inhibited collagen synthesis to normal, but in wound chambers a daily application of 5 μg EGF to methylprednisolone-treated rats (in an albumin carrier) restores collagen and matrix protein levels to normal[74]. EGF increased fibroblast numbers but did not stimulate collagen synthesis per cell.

Local irradiation impairs wound healing but does not affect circulating white cell counts. A single application of 2–10 μg PDGF in a collagen vehicle partially reverses the surface irradiation wound healing deficit in the skin of rats 7 days after creation of the wound, but does not reverse the wound healing deficit seen with total body irradiation[25].

Cytotoxic treatment decreases the circulating white cell count and impairs formation of granulation tissue in a wound chamber. Adriamycin® (Farmitalia Carlo Elba Ltd., St. Albans, UK) treatment has been demonstrated to reduce the level of TGF-β and PDGF-like activity in aliquots of wound fluid removed from wound chambers. Injection of TGF-β into the wound chamber returns granulation tissue formation to normal levels[75]. Incisional wound healing is impaired by Adriamycin treatment and the strength of wounds is returned to normal by a single intraincisional application of 2 μg TGF-β or 50 ng TNF in a collagen vehicle[26,58]. A study of RNA from wounds of doxorubicin-treated rats using specific complementary DNA probes indicates decreased gene expression of type I procollagen mRNA and TGF-β mRNA at 7 days. Exogenous application of 2 μg TGF-β returned procollagen mRNA levels to normal[76].

Several investigators have studied the effects of growth factors on wound healing in diabetic animals. In a Hunt-Schilling chamber, exogenous PDGF restores deficient granulation tissue formation to normal in diabetic rats[51]. In female diabetic mice, 0·5 μg recombinant bFGF applied locally to full-thickness punch biopsy wounds once a day increases thickness, infiltrating cell number and capillary number in the granulation tissue formed[77]. A combination of topically applied EGF and insulin is more effective than EGF alone in stimulating collagen synthesis and collagenase activity in polytetrafluoroethylene cylinders implanted in diabetic rats[78]. In these experiments wound maturation is enhanced by EGF, as demonstrated by earlier replacement of type III by type I collagen in EGF-treated wounds.

Other tissues

The maturation of intestinal wounds differs from the maturation of skin wounds, and this is mainly reflected in the rate of accumulation of collagen[79]. Fibroblasts are present in low numbers in intestinal submucosa and collagen is generated by smooth muscle cells. TGF-β augments collagen and matrix synthesis from intestinal smooth muscle cells *in vitro*, so it is likely that modulation of wound repair in intestine differs from that in skin[80]. The gain in strength of intestinal wounds is far more rapid than in skin, whether assessed by measurement of anastomotic bursting pressure or the breaking strength of linear enterotomy wounds. Collagenase activity plays an important role in the first few days, and this enzyme may be controlled by local secretion and paracrine effects of growth factors[81]. Continuous intraperitoneal delivery of EGF (0·5 μg/kg daily) increases the tensile strength of linear enterotomy wounds by 20 per cent 5 days after wounding in stomach, ileum and colon, and this is accompanied by an increase in cellularity[82]. In the rabbit stomach, topical application of TGF-β (0·1–2 μg per wound) to partial-thickness (excluding mucosa) longitudinal incisions accelerates wound breaking strength by 4 days. PDGF at 10 μg per wound does not enhance gastric wound strength but increases cellular influx, whereas TGF-β does not affect cellularity[83]. A local application of TGF-β (5 μg per wound) in a collagen suspension reverses the impairment of breaking strength induced by steroids in healing longitudinal pig enterotomy wounds, although no differences in wound cellularity occur[84].

Human studies

In anticipation of clinical application of growth factors, the US Food and Drug Administration has discussed guidelines to be adopted before phase I clinical studies[85]. The first clinical trials with EGF were negative; daily application of 5 μg EGF to suction blisters on the anterior abdominal wall did not improve healing nor did local EGF affect epithelial healing after penetration keratoplasty[86,87]. These results may have been due to lack of purity before production of growth factors using recombinant DNA methods became available. Alternative reasons for this negative effect have been investigated in the alkali-burned cornea of rats; a lack of adherence of regenerated epithelium to underlying stroma has been shown[88]. This is clearly a problem which will have to be addressed in the future. A clinical trial using skin graft donor sites has demonstrated that 10 μg/ml EGF, applied in an antibiotic cream at each wound dressing, reduces the length of time to healing by between 1 and 1·5 days[69].

The future

Before any reasoned manipulation of normal wound healing is possible, it will be necessary to develop a conceptual cascade that explains the interaction between the cellular elements and messenger peptides within the healing milieu. Much of the experimental work described involves the assessment of healing using parameters that are very theoretical. It will be necessary to develop and test peptide applications in experimental models which more closely resemble a given clinical situation. Clinical benefit in patients may be difficult to demonstrate except in situations where wound failure is a significant hazard, allowing its improvement to be measured more easily. It is for this reason that we believe the manipulation of states of impaired healing will represent the first application of locally applied growth factors.

The next technical step in the application of growth factors at wound sites will be adsorption of growth factors into wound suture material or into carrier vehicles that can be applied to wounds. Such materials will have a wide application in incisional and intestinal wounds. The suture industry has progressed from using natural products such as silk and linen, which are not entirely biocompatible or bioabsorbable, to the use of reabsorbable biopolymers. The next logical step is a wound-healing spray or a suture which could release peptide growth factors at the wound site, to improve and accelerate healing. There is an ever-increasing demand from patients for surgical procedures which return them to the community and economic productivity at the earliest opportunity. A wound biomaterial which shortens the length of time to healing and to return of function will achieve this objective.

References

1. Hunt TK, LaVan FB. Enhancement of wound healing by growth factors. *N Engl J Med* 1989; **321**: 111–12.

2. Brown JM, Harken AH, Sharefkin JB. Recombinant DNA and surgery. *Ann Surg* 1990; **212**: 178–86.
3. Roberts AB, Flanders KC, Heine IU, Jakowlew, S, Sporn MB. Transforming growth-factor-β: multifunctional regulator of differentiation and development. *Philos Trans R Soc Lond [Biol]* 1990; **327**: 145–54.
4. Heldin C-H, Westermark B. Platelet-derived growth factor: mechanism of action and possible *in vivo* function. *Cell Reg* 1990; **1**: 555–66.
5. Rothe M, Falanga V. Growth factors: their biology and promise in dermatological diseases and tissue repair. *Arch Dermatol* 1989; **125**: 1390–8.
6. tenDijke P, Iwata IK. Growth factors for wound healing. *Biotechnology* 1989; **7**: 793–8.
7. Wahl SM, Wong H, McCartney-Francis N. Role of growth factors in inflammation and repair. *J Cell Biochem* 1989; **40**: 193–9.
8. Assoian RK, Komoriya A, Meyers CA, Miller DM, Sporn MB. Transforming growth factor-β in human platelets: identification of a major storage site, purification and identification. *J Biol Chem* 1983; **258**: 7155–60.
9. Kaplan DR, Chao FC, Stiles CD, Antoniades HN, Scher DC. Platelet alpha granules contain a growth factor for fibroblasts. *Blood* 1979; **53**: 1043–8.
10. Savage AP, Chatterjee VK, Gregory H, Bloom SR. Epidermal growth factor in blood. *Regul Pept* 1986; **16**: 199–206.
11. Oka Y, Orth DN. Human plasma epidermal growth factor/β-urogastrone is associated with blood platelets. *J Clin Invest* 1983; **72**: 249–59.
12. Pierce GF. Macrophages: important physiologic and pathologic sources of polypeptide growth factors. *Am J Resp Cell Mol Biol* 1990; **2**: 233–4.
13. Lewis C, McCarthy SP, Lorenzen J, McGee JO'D. Heterogenicity among human mononuclear phagocytes in their secretion of lysosome, interleukin 1 and type-β transforming growth factor; quantitative analysis at the single cell level. *Eur J Immunol* 1989; **19**: 2037–43.
14. Rappollee DA, Mark D, Banda MJ, Werb Z. Wound macrophages express TGF-α and other growth factors in vivo: analysis by mRNA phenotyping. *Science* 1988; **241**: 708–12.
15. Leibovich SJ, Polverini PJ, Shephard HM, Wiseman DN, Shively V, Nusier N. Macrophage-induced angiogenesis is mediated by tumour necrosis factor-alpha. *Nature* 1987; **329**: 630–2.
16. Baird A, Mormede P, Bohlen P. Immunoreactive fibroblast growth factor in cells of peritoneal exudate suggests its identity with macrophage derived growth factor. *Biochem Biophys Res Commun* 1985; **126**: 358–64.
17. Hunt TK. Prospective; a retrospective perspective on the nature of wounds. *Prog Clin Biol Res* 1988; **266**: xiii–xx.
18. Sporn MB, Roberts AB, Wakefield LM, de Crombrugghe B. Some recent advances in the chemistry and biology of transforming growth factor beta. *J Cell Biol* 1987; **105**: 1039–45.
19. Bauer EA, Cooper TW, Huang JS, Altman J, Deuel TF. Stimulation of *in vitro* human skin collagenase expression by platelet derived growth factor. *Proc Natl Acad Sci USA* 1985; **82**: 4132–6.
20. Fukamizu H, Grinnell F. Spatial organisation of extracellular matrix and fibroblast activity: effects of serum, TGF-β and fibronectin. *Exp Cell Res* 1990; **8** 190: 276–82.
21. Bernfield M, Sanderson RD. Syndecan, a developmentally regulated cell surface proteoglycan that binds extracellular matrix and growth factors. *Philos Trans R Soc Lond [Biol]* 1990; **327**: 171–86.
22. Editorial. Fibroblast growth factors: a time to take note. *Lancet* 1990; **ii**: 777–8.
23. Broadley KN, Aquino AM, Hicks B *et al.* Growth factors bFGF and TGFβ accelerate the rate of wound repair in normal and in diabetic rats. *Int J Tissue React* 1988; **6**: 345–53.
24. Pierce GF, Mustoe TA, Lingelbach J, Masakowki VR, Gramates P, Deuel TF. Transforming growth factor β reverses the glucocorticoid-induced wound-healing deficit in rats: possible regulation in macrophages by platelet-derived growth factor. *Proc Natl Acad Sci USA* 1989; **86**: 2229–33.
25. Mustoe TA, Purdy J, Gramates P, Deuel TF, Thomason A, Pierce GF. Reversal of impaired wound healing in irradiated rats by platelet-derived growth factor BB. *Am J Surg* 1989; **158**: 345–50.
26. Curtsinger LJ, Pietsch JD, Brown GL *et al.* Reversal of Adriamycin-impaired wound healing by transforming growth factor-beta. *Surg Gynecol Obstet* 1989; **168**: 517–22.
27. Whal SM, Hunt DA, Wakefield LM. Transforming growth factor-β induces monocyte chemotaxis and growth factor production. *Proc Natl Acad Sci USA* 1987; **84**: 5788–92.
28. Deuel TF, Senior RM, Huang JS, Griffin GL. Chemotaxis of monocytes and neutrophils to platelet derived growth factor. *J Clin Invest* 1982; **69**: 1046–52.
29. Buckley-Sturrock A, Woodward SC, Senior RM, Griffin GL, Klagsburn H, Davidson JM. Differential stimulation of collagenase and chemotactic activity in fibroblasts derived from rat wound repair tissue and human skin by growth factors. *J Cell Physiol* 1989; **138**: 70–8.
30. Postlethwaite AE, Keski-Oja J, Moses HL, Kang AH. Stimulation of the chemotactic migration of human fibroblasts by transforming growth factor beta. *J Exp Med* 1987; **165**: 251–6.
31. Seppa H, Grotendorst G, Seppa S, Schiffman E, Martin GR. Platelet derived growth factor is chemotactic for fibroblasts. *J Cell Biol* 1982; **92**: 584–8.
32. Narayanan AS, Page RC, Swanson J. Collagen synthesis by human fibroblasts: regulation by transforming growth factor-β in the presence of other inflammatory mediators. *Biochem J* 1989; **260**: 463–9.
33. Fine A, Polis CF, Smith BD, Goldstein RH. The accumulation of type I collagen mRNA in human embryonic lung fibroblasts stimulated by transforming growth factor beta. *Connect Tissue Res* 1990; **24**: 237–47.
34. Ignotz RA, Massague J. Transforming growth factor β stimulates the expression of fibronectin and collagen and their incorporation into extracellular matrix. *J Biol Chem* 1986; **269**: 4337–45.
35. Penttinen RP, Koybayashi S, Bornstein P. Transforming growth factor beta increases mRNA for matrix proteins both in the presence and absence of changes in the mRNA stability. *Proc Natl Acad Sci USA* 1988; **85**: 1105–8.
36. Roberts CJ, Birkenmeier TM, McQuillan JJ. Transforming growth factor β stimulates the expression of fibronectin and of both units of the fibronectin receptor by cultured dermal fibroblasts. *J Biol Chem* 1988; **263**: 4586–92.
37. Narayanan AS, Page RC, Swanson J. Collagen synthesis by human fibroblasts. *Biochem J* 1989; **260**: 464–9.
38. Heldin P, Laurent TC, Heldin CH. Effect of growth factors on hyaluron synthesis in cultured human fibroblasts. *Biochem J* 1989; **258**: 919–22.
39. Overall CM, Wrana JL, Sokek J. Transforming growth factor β regulation of collagenase, 72 kda-progelatins and PA1 expression in rat bone cell populations and human fibroblasts. *Connect Tissue Res* 1989; **29**: 289–94.
40. Hata R, Sunada H, Arai K, Sato T, Ninomiya Y, Nagai Y. Regulation of collagen metabolism and cell growth by epidermal growth factor and ascorbate in cultured human skin fibroblasts. *Eur J Biochem* 1988; **173**: 261–7.
41. Terranova VP, Diflorio R, Lyall RM, Hic S, Fressal R, Macaig T. Human endothelial cells are chemotactic to endothelial cell growth factor and heparin. *J Cell Biol* 1985; **101**: 2330–4.
42. Finesmith TH, Broadley KN, Davidson JM. Fibroblasts from wounds of different stages of repair vary in their ability to contract a collagen gel in response to growth factors. *J Cell Physiol* 1990; **144**: 99–107.
43. Grotendorst GR, Soma Y, Takehar K, Charette M. EGF and TGF-α are potent chemoattractants for endothelial cells and EGF-like peptides are present at sites of tissue regeneration. *J Cell Physiol* 1989; **139**: 617–23.
44. Cromak DT, Sporn MB, Roberts AB. Transforming growth factor-β levels in rat wound chambers. *J Surg Res* 1987; **42**: 622–8.
45. Grotendorst GR, Grotendorst CA, Gilman T. Production of growth factors (PDGF and TGF-β) at the site of tissue repair. *Prog Clin Biol Res* 1988; **266**: 47–54.
46. Buckley AJM, Davidson DC, Kamerath TB, Wolt TB, Woodward SC. Sustained release of epidermal growth factor accelerates wound repair. *Proc Natl Acad Sci USA* 1985; **82**: 7340–5.
47. Laato M, Niinikoski J, Gerdin B, Lebel L. Stimulation of wound healing by epidermal growth factor: a dose-dependent effect. *Ann Surg* 1986; **203**: 379–81.
48. Buckley A, Davidson JM, Kamerath CD, Woodward SC. Epidermal growth factor increases granulation tissue formation dose dependently. *J Surg Res* 1987; **43**: 322–8.
49. Laato M, Kahari V-M, Niinikoski J, Vuorio E. Epidermal growth factor increases collagen production in granulation tissue by stimulation of fibroblast proliferation and not by activation of

procollagen genes. *Biochem J* 1987; **247**: 385–8.

50. Sprugel KH, McPherson JM, Clowes AW, Ross R. Effects of growth factors *in vivo*: I. Cell ingrowth into porous subcutaneous chambers. *Am J Pathol* 1987; **129**: 601–13.

51. Grotendorst GR, Martin CR, Pencev D, Soden J, Harvey AK. Stimulation of granulation tissue formation by platelet-derived growth factor in normal and diabetic rats. *J Clin Invest* 1985; **76**: 2323–9.

52. Folkman J, Klagsbrum M. Angiogenesis factors. *Science* 1987; **235**: 442–7.

53. Mahadevan V, Hart IR, Lewis GP. Factors influencing blood supply in wound granuloma quantitated by a new *in vivo* technique. *Cancer Res* 1989; **49**: 415–19.

54. Brown GL, Curtsinger LJ, White M *et al.* Acceleration of tensile strength of incisions treated with epidermal growth factor and transforming growth factor-beta. *Ann Surg* 1988; **208**: 788–94.

55. Mustoe TA, Pierce GF, Thomason A, Gramates P, Sporn MB, Deuel TF. Accelerated healing of incisional wounds in rats induced by transforming growth factor-β. *Science* 1987; **237**: 1333–6.

56. Pierce GF, Mustoe TA, Lingelbach J *et al.* Platelet derived growth factor and transforming growth factor-β enhance tissue repair activities by unique mechanisms. *J Cell Biol* 1989; **109**: 430–3.

57. Mooney DP, O'Reilly M, Gamelli RL. Tumor necrosis factor and wound healing. *Ann Surg* 1990; **211**: 124–9.

58. McGee GS, Davidson JM, Buckley A *et al.* Recombinant basic fibroblast growth factor accelerates wound healing. *J Surg Res* 1988; **45**: 145–53.

59. Slavin J, Kingsnorth AN. Fibroblast growth factor in a slow release vehicle accelerates incisional wound healing. *Br J Surg* 1991; Abstract (in press).

60. Lynch SE, Nixon JC, Colvin RB, Antoniades HN. Role of platelet-derived growth factor in wound healing: synergistic effects with other growth factors. *Proc Natl Acad Sci USA* 1987; **84**: 7696–700.

61. Quaglino D, Nanney LB, Kennedy R, Davidson JM. Transforming growth factor-β stimulates wound healing and modulates extracellular matrix gene expression in pig skin. I. Excisional wound model. *Lab Invest* 1990; **63**: 307–19.

62. Lynch SE, Colvin RB, Antoniades HN. Growth factors in wound healing: single and synergistic effects on partial thickness porcine skin wounds. *J Clin Invest* 1989; **84**: 640–6.

63. Ksander GA, Ogawa Y, Chu GH, McMullin H, Rosenblatt JS, McPherson JM. Exogenous transforming growth factor-beta 2 enhances connective tissue formation and wound strength in guinea pig dermal wounds healing by secondary intent. *Ann Surg* 1990; **211**: 288–94.

64. Nanney LB. Epidermal and dermal effects of epidermal growth factor during wound repair. *J Invest Dermatol* 1990; **94**: 624–9.

65. Brown GL, Curtsinger L, Brightwell JR *et al.* Enhancement of epidermal regeneration by biosynthetic epidermal growth factor. *J Exp Med* 1986; **163**: 1319–24.

66. Schultz GS, White M, Mitchell R *et al.* Epithelial wound healing enhanced by transforming growth-factor-α and vaccinia growth factor. *Science* 1987; **235**: 350–1.

67. van Obberghen-Schilling E, Roche NS, Flanders RC, Sporn MB, Roberts AB. Transforming growth factor beta-1 positively regulates its own expression in normal and transformed cells. *J Biol Chem* 1988; **263**: 7741–7.

68. Liebovich SJ, Ross R. The role of the macrophage in wound repair. *Am J Pathol* 1975; **78**: 71–91.

69. Raghow R, Gassage D, Kanga H. Pretranslational regulation of type 1 collagen, fibronectin and a 50 KDalton non collagenous protein by dexamethasone in rat fibroblasts. *Am J Biol Chem* 1986; **261**: 4677–84.

70. Cockayne D, Sterling KM, Shull S, Mintz KP. Glucocorticoids decrease the synthesis of type 1 procollagen mRNA. *Biochemistry* 1986; **25**: 3202–8.

71. Oikarinem J, Ryhanem L. Cortisol decreases the concentration of translatable type 1 procollagen mRNA species in the developing chick. *Biochem J* 1981; **198**: 519–23.

72. Niimi S, Kayakawa T, Uchida E, Tanaka A. Effects of glucocorticoids on DNA synthesis stimulated by growth factors in cultured rat skin fibroblasts. *Chem Pharm Bull* 1990; **38**: 1633–8.

73. Gronwald RGK, Seifert RA, Bowen-Pope DF. Differential regulation of expression of two platelet-derived growth factor subunits by transforming growth factor-beta. *J Biol Chem* 1989; **264**: 8120–5.

74. Laato M, Heino J, Kahaari V-M, Niinikoski J, Gerdin B. Epidermal growth factor (EGF) prevents methylprednisolone-induced inhibition of wound healing. *J Surg Res* 1989; **47**: 354–9.

75. Lawrence WT, Norton JA, Sporn MB, Gorschboth C, Grotendorst GR. The reversal of adriamycin induced healing impairment with chemoattractants and growth factors. *Ann Surg* 1986; **203**: 142–7.

76. Salomon GD, Kasid A, Bernstein E, Buresh C, Director E, Norton JA. Gene expression in normal and doxorubicin-impaired wounds: importance of transforming growth factor-beta. *Surgery* 1990; **108**: 318–23.

77. Tsuboi R, Rifkin DB. Recombinant basic fibroblast growth factor stimulates wound healing in healing-impaired db/db mice. *J Exp Med* 1990; **172**: 245–51.

78. Hennessey PJ, Black T, Andrassy RJ. Epidermal growth factor and insulin act synergistically during diabetic healing. *Arch Surg* 1990; **125**: 926–9.

79. Hendriks T, Mastboom WJB. Healing of experimental intestinal anastomoses: parameters for repair. *Dis Colon Rectum* 1990; **33**: 891–901.

80. Graham MF, Bryson GR, Diegelmann RF. Transforming growth factor β1 selectively augments collagen synthesis by human intestinal smooth muscle cells. *Gastroenterology* 1990; **99**: 447–53.

81. Chowchat NL, Savage FJ, Hembry RM, Boulos PB. Role of collagenase in colonic anastomoses: a reappraisal. *Br J Surg* 1988; **75**: 330–4.

82. Kingsnorth AN, Vowles R, Nash JRG. Epidermal growth factor increases tensile strength in intestinal wounds in pigs. *Br J Surg* 1990; **77**: 409–12.

83. Mustoe TA, Landes A, Cromach DT *et al.* Differential acceleration of healing of surgical incisions in the rabbit gastrointestinal tract by platelet-derived growth factor and transforming growth factor, type beta. *Surgery* 1990; **108**: 24–30.

84. Slavin J, Nash R, Kingsnorth AN. Transforming growth factor beta reverses the steroid inhibition of intestinal wound healing. *Br J Surg* 1991; Abstract (in press).

85. Weissinger J. Non-clinical regulatory considerations for wound-healing growth factors. *Drug Dev Res* 1990; **19**: 275–83.

86. Greaves MW. Lack of effect of topically applied epidermal growth factor (EGF) on epidermal growth in man *in vivo*. *Clin Exp Dermatol* 1980; **5**: 101–3.

87. Kandarakis AS, Page C, Kaufman HE. The effect of epidermal growth factor on epithelial healing after penetrating keratoplasty in human eyes. *Am J Ophthalmol* 1984; **98**: 411–15.

88. Singh G, Foster CS. Epidermal growth factor in alkali-burned corneal epithelial wound healing. *Am J Ophthalmol* 1987; **103**: 802–7.

89. Brown GL, Nanney LB, Griffen J *et al.* Enhancement of wound healing by topical treatment with epidermal growth factor. *N Engl J Med* 1989; **321**: 76–8.

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Review

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Sutureless intestinal anastomoses

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Sutureless intestinal anastomoses can be achieved either by compression, where two inverted rings of bowel are compressed by a hollow circular device that subsequently sloughs away and is passed anally, or by the use of tissue glues or laser welding. Compression devices used clinically with success are the Valtrac® biofragmentable anastomotic ring, the polypropylene rings described by Rosati and the AKA guns. Glued anastomoses have only been used in animals and seem to be unsafe. However, laser-welded intestinal anastomoses appear highly promising in experimental studies and further development of this technique is warranted.

There can be few surgeons who would feel comfortable constructing an intestinal anastomosis without the use of either sutures or staples. A 'sutureless' anastomosis sounds inherently unsafe; and yet there are cogent reasons why such a technique may not only be safe, but may be preferable to more standard techniques. This review assesses different types of clinical and experimental sutureless intestinal anastomoses.

The concept of an anastomosis without sutures is not new. In 1826 Denans introduced an intraluminal device over which the cut ends of bowel were approximated[1]. Further mechanical devices were designed by Bonnier in 1885[1] and by Murphy in 1892[2]. Murphy's 'button' consisted of two metal rings which trapped the cut ends of the transected bowel, bringing them into apposition and allowing healing. The trapped bowel was rendered ischaemic and eventually sloughed, releasing the button into the faecal stream. Although the device was quite widely used, early problems of obstruction arose due to the narrow lumen of the button and later obstruction because of anastomotic stenosis. In 1893 Senn[3] stipulated: 'If any internal aids to circular suturing are used they should be composed of absorbable materials and employed in such a way as to not produce marginal gangrene and with a central opening large enough to allow free faecal circulation'. Earlier in this century Boerema developed a spring-loaded implement based on similar principles to the Murphy button[4]. Although good results were reported in upper gastrointestinal anastomoses, the procedure was never generally adopted.

Sutures and anastomotic wound healing

All wounds, including intestinal anastomoses, go through several stages of healing[5,6]. It is usual to consider these stages in three overlapping phases: the lag phase, an acute inflammatory response which clears the wound of debris (0–4 days); the phase of fibroplasia, when fibroblasts proliferate and lay down immature collagen (3–14 days); and the phase of maturation, while collagen remodels (10–80 days or more). During the lag phase the wound is extremely weak and is reliant on additional support, e.g. sutures. Gain in wound strength is rapid during the phase of fibroplasia and by the end of this period the intestinal anastomosis no longer requires reinforcement.

Sutures or staples are currently used to support intestinal anastomoses. However, the vast majority of materials used are either non-absorbable or are absorbed a substantial time after they have fulfilled their useful purpose. We need to consider the potential disadvantages of suture and staple usage.

Traumatic insertion

Passage of a needle through the bowel wall is traumatic due to transection of structures in its path[7]. On occasion, interference to the local blood supply may arise. Damage to the submucosa occurs with rougher surfaced suture materials such as catgut, silk and Dexon® (Davis and Geck, Gosport, UK)[8]. As this layer is important for anastomotic integrity, traumatic damage is a potential hazard.

Effect on healing

All sutures and staples induce an acute inflammatory response which subsides within a week[9]. With non-absorbable sutures this is followed by a fibroplastic response with formation of a thin collagen sheath around the suture. Chronic inflammation persists around absorbable sutures until absorption is complete, although those that take months to disappear also evolve a collagen sheath[10,11]. In experimental skin wounds, 40 days after suture removal fibrosing granulomatous tissue is still evident along the suture tract[7]. Associated inflammation is more severe and prolonged than that related to the healing wound itself.

Exaggerated and persisting inflammation is bad for wound healing. Comparison of intestinal suturing techniques has shown that methods which elicit less inflammation regain anastomotic strength at a faster rate[12,13], and the tensile strength of taped wounds is greater than that of sutured wounds[14]. Steri-Strip® (3M, Loughborough, UK) applied to skin wounds gives better clinical results than sutures[15].

Increased anastomotic sepsis

Luminal bacteria may adhere to the suture and traverse the bowel. Experimental work has shown that bacterial adherence to suture materials plays a role in the induction of surgical infection[16,17]. Indeed, the idea of perianastomotic infection arising from bacteria that had traversed the bowel wall along suture tracks, which might rupture back into the anastomosis thereby 'causing' an anastomotic leak, gave some of the intellectual impetus to extramucosal serosubmucosal suturing (the 'Matheson technique'[18]).

Suture implantation metastases

It is believed that suture implantation of exfoliated colorectal cells is one cause of anastomotic recurrence. Injection of tumour cells into the gut before enterotomy and repair causes suture line tumours in experimental animals[19] and confirmation that sutures can transfer carcinoma cells to other sites has been shown[20]. Studies have also found that although tumour cells cannot grow on intact colonic mucosa, transfer of cells into the bowel wall via suture material does result in anastomotic tumours[21,22]. It has since been shown that tumour cells are adherent to suture material[23], particularly braided sutures[24], and the relevance of these findings has been confirmed by tumour growth studies.

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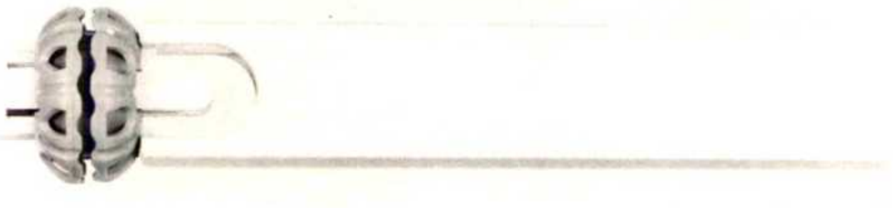


Figure 1 *Valtrac® biofragmentable anastomotic ring mounted on introducer. The ring is in the closed position and demonstrates the scalloped margin and a 2-mm gap*

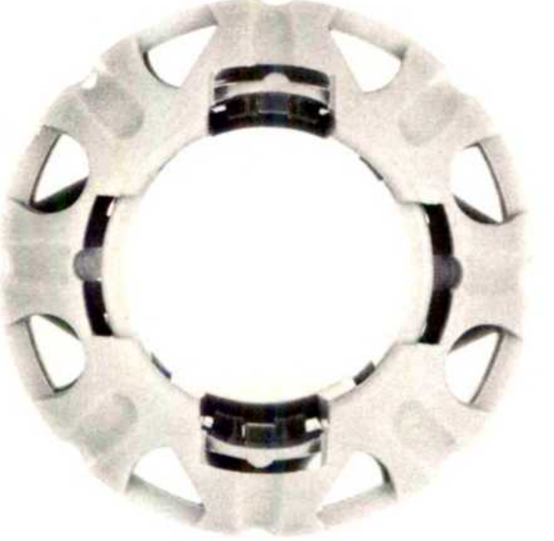


Figure 2 *End view of Valtrac® to show central lumen 14 mm smaller than the external diameter*

Enhanced metachronous cancer risk

In experimental animals given carcinogens, tumours cluster around colonic anastomoses[25–28] and the tumour yield is influenced by the nature of the suture used[29,30]. Furthermore, an experimental sutureless technique has shown a lower tumour yield than sutured anastomoses[6,7].

These theoretical disadvantages to the use of sutures and staples in intestinal anastomoses have provided stimulus for the development of alternative, or sutureless, techniques.

Sutureless techniques

Clinical: compression devices

The following devices all utilize the principle of compression to unite bowel ends. With time, the compressed bowel edges necrose, releasing the device into the faecal stream, leaving behind a healing and sutureless intestinal wound.

Biofragmentable anastomotic ring. The Valtrac® biofragmentable anastomotic ring (BAR) was invented by Hardy *et al.*[31] in conjunction with Davis and Geck, and was first introduced in 1985 (*Figures 1* and *2*). It is made from absorbable polyglycolic acid and 12·5 per cent barium sulphate which renders it radio-opaque. The two components interdigitate on a central frame; a 6-mm gap is seen in the open position, and a 1·5–2-mm gap when closed. Compromise of the intramural blood supply is minimized by the scalloped rim. As with existing staple guns a variety of sized heads are available: 28, 31 and 34 mm, each 14 mm larger than the internal lumen. The BAR with inserter is advanced into one end of the bowel and secured with a purse-string suture. After removal of the inserter, the opposite end of the BAR is manoeuvred into the other end of the bowel and held with a second purse-string. The BAR is then snapped shut to achieve anastomosis. After healing the BAR fragments and is passed in the faeces.

Immediate anastomotic strength is substantially higher with the BAR than with either stapled or sutured anastomosis[31] and is similar thereafter[32]. A lesser degree of foreign body reaction or microabscess formation is seen with the BAR[31] and at 1 year smaller amounts of granulation tissue are noted compared with conventional anastomoses[32], suggesting improved healing.

The results of several randomized prospective trials with the BAR in elective colonic surgery are now available[33–35]. Intraoperative problems due to placement of the BAR arose in 6–10 per cent of cases. These problems were often related to using a device too large and generally arose during the 'learning curve'. Mean performance time was less with the BAR (22 min) than with sutures (37 min) or staples (33 min). Perioperative morbidity and mortality rates were comparable to those found in sutured and stapled groups. No postoperative complications could be attributed directly to the BAR. The fragments were passed between 14 and 23 days, unnoticed by the majority of patients[33,36], although one ring impacted in the anal canal[34].

The major drawback with the BAR at present is that no endoanal introducer exists, effectively limiting its use to anastomoses above 10 cm from the anal margin.

AKA guns. A gun has been designed in the USSR which releases intraluminally a spring-loaded head to hold the bowel together without staples or sutures (*Figures 3–6*). Passage of the head occurs at about 8 days, once the rim of tissue held under pressure between the two rings has necrosed. This device incorporates many of the features of staple guns, including an anvil which can be advanced and retracted to allow accurate purse-string closure and bowel approximation, a circular knife which cuts away the purse-string and excess tissue, and permits endoanal anastomosis. A variety of different sized heads are manufactured and the gun is available in a reusable (AKA 2) or disposable (AKA 4) form. We have recently been made aware of a new version with a flexible shaft and biofragmentable compression device (AKA 6), but have not had the opportunity to examine it.

AKA anastomosis has been studied in 140 patients following resection of the distal colon or rectum[37,38]. Anastomotic leakage occurred in eight patients (5·7 per cent), in three of whom it was detected only by Gastrografin® (Schering, UK) enema. Excluding the 16 patients with a defunctioning colostomy, the leakage rate was 6·4 per cent. No complications due specifically to the technique were noted.

Polypropylene rings. Another intraluminal device has been invented by Rosati and further refined by Deknatel (division of Pfizer Incorporated, Fall River, Massachusetts, USA) as the anastomotic compression button (ACB)[39]. This comprises three polypropylene rings which are configured to interlock on release from a mechanical introducer, which once again is based upon the staple gun. After firing the ACB, a circular knife cuts through the purse-string on both bowel edges, leaving a water-tight inverted serosa–serosa anastomosis. As with the other intraluminal devices, the rings pass into the faecal stream following necrosis of the compressed bowel.

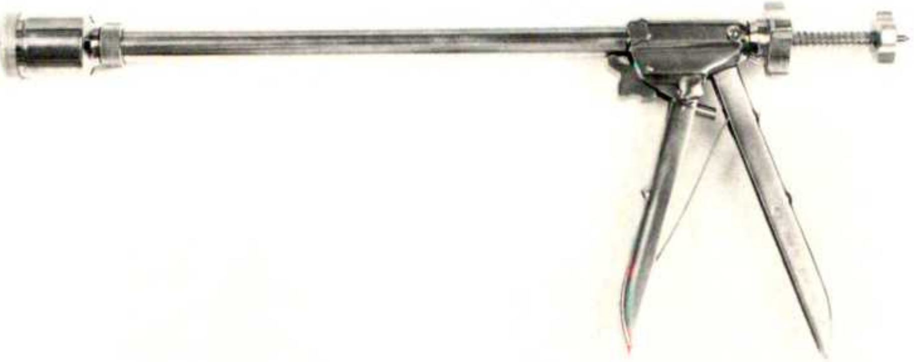


Figure 3 *AKA 2 compression anastomosis gun*

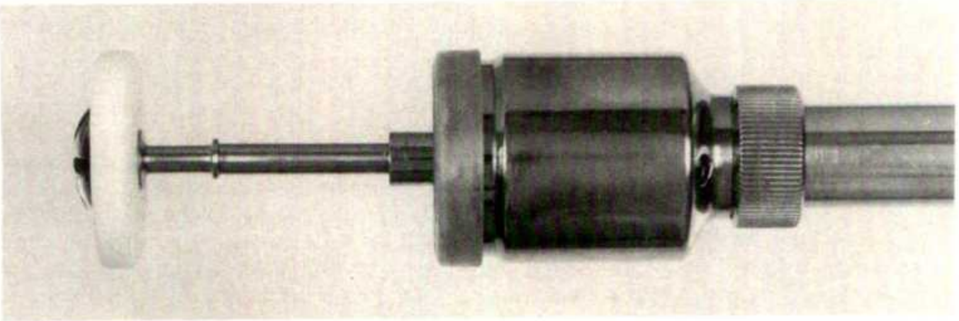
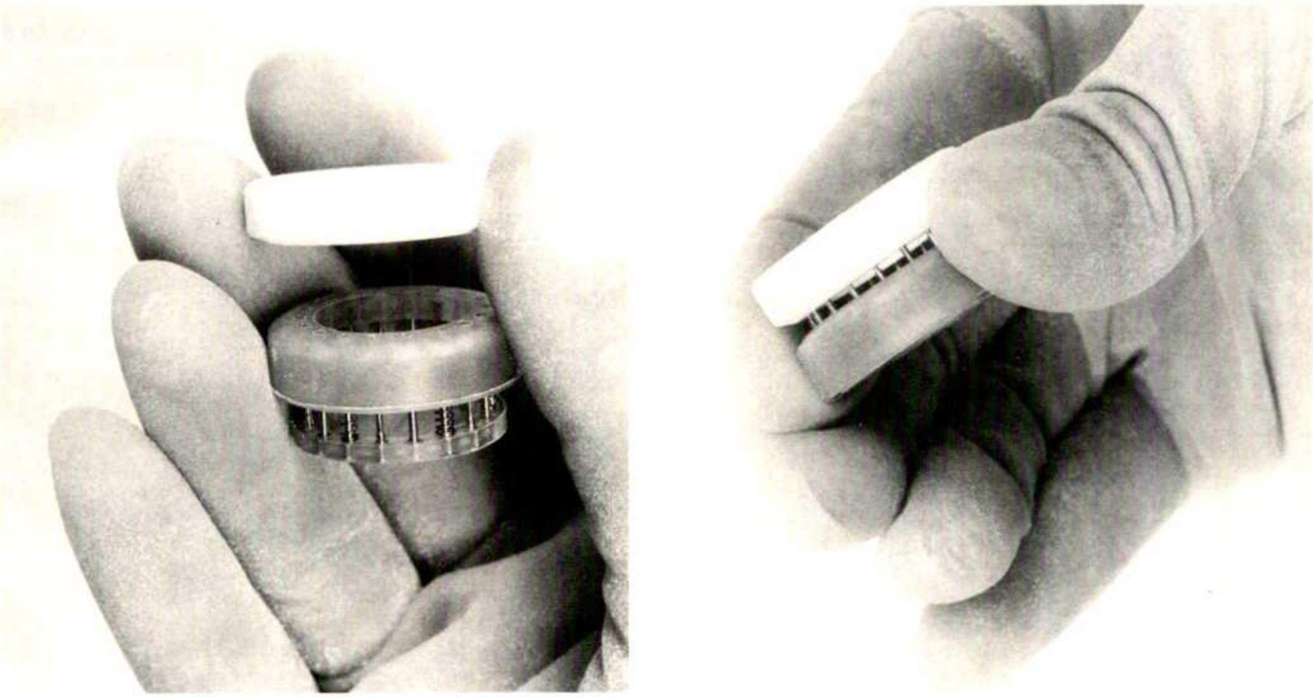


Figure 4 *AKA 2: close-up of head with anvil advanced. On the left is the white plastic ring; on the right is the combined guillotine and spring-loaded device. The rim on the shaft facilities tying of purse-strings*



a

b

Figure 5 **a** *Side view of compression components before firing to show spring-loaded pins.* **b** *Side view of compression components after firing. Considerable pressure is being applied to prise them open and demonstrate the pins*

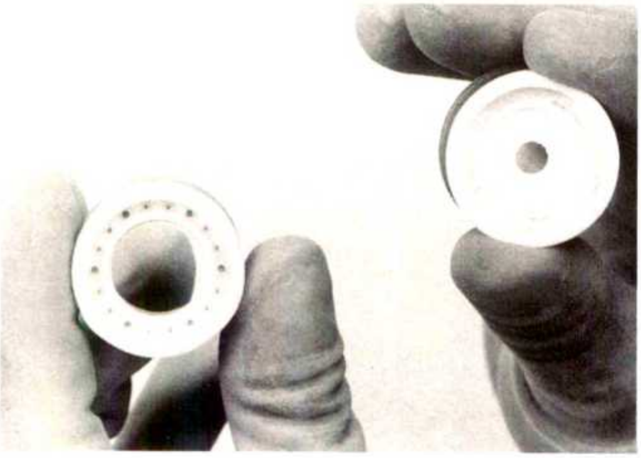


Figure 6 *On the right is the white plastic ring (seen mounted on shaft in* Figure 2) *before the device has been fired. On the left, the guillotine has created a central lumen and the joining pins can be seen*

Experimental studies in dogs showed that mucosal blood flow, bursting pressure and anastomotic indices were identical to those observed with stapled anastomoses. In addition, with the ACB there was a lesser degree of ulceration, fibrosis and inflammation, with more rapid re-epithelialization[39,40]. Reported clinical experience is small. In a series of 13 colonic anastomoses one subclinical leak was noted (8 per cent)[39]. Passage of the rings occurred after a mean of 11·2 days, without discomfort.

Magnetic rings. It is more than a decade since the magnetic ring anastomotic apparatus was described[41]. The device is similar to the AKA described above except that the two component rings contain 'matrix' (polymer-bonded rare earth cobalt) magnets which apply progressive compression to the trapped bowel edges, rather than springs. An important part of this technique was submucosal apposition, requiring separation of the muscle from the mucosa and submucosa for 4 mm. Twenty-one patients underwent magnetic anastomosis after sigmoid resection or low anterior resection[42]. Clinical leaks occurred in two patients (10 per cent); one patient needed reoperation. The rings cut through after a mean of 9 days. No stenoses were evident by 1 year; indeed, anastomotic scarring was minimal or absent. Since then there have been no further reports in the literature and we suspect the technique may have foundered for lack of commercial sponsorship.

Experimental: adhesive anastomoses and laser welding

Adhesive anastomoses. The application of glues to construct intestinal anastomoses was first investigated in experimental animals during the 1960s. Initial studies were performed in dogs using methyl-2-cyanoacrylate (a monomer that is catalysed to the solid state by water) plus a thickening agent and plasticizer[43–45]. In all reports there was poor adhesion between glue and mucosa, which was therefore scraped away to allow application of the glue directly to the denuded submucosa. At first all anastomoses were everted and uniformly poor results were obtained. In the small bowel, anastomotic failure (usually fatal) was noted in 9–33 per cent[44–47]. Most commonly failure was due to anastomotic necrosis and subsequent leakage but 4 per cent of animals died from obstruction[47]. Results in the colon were even worse, with a mortality rate from anastomotic leakage of 29–38 per cent[45,46]. Similar results were obtained in rats with a mortality rate of 23 per cent following colon transection and anastomosis[48]. An invagination procedure was designed by Linn *et al.*[43] in which 2·5 cm of mucosa was stripped from the distal limb of the bowel, the glue was applied to the submucosa and coapted to the distal 2·5 cm of the proximal bowel. Although this reduced the fatalities from leakage, 12 per cent of the animals developed strictures. Later studies investigated isobutyl cyanoacrylate, because it was believed that lengthening the alkoxyl group of the 2-cyanoacrylic acid ester would reduce the histotoxicity and consequent intestinal necrosis[49]. Results were not improved, with a mortality rate of 13 per cent following invagination anastomosis and 25–57 per cent after conventional anastomoses[50–52]. Not surprisingly these techniques were never attempted in humans and have now been abandoned.

The problems of direct histotoxicity do not apply to fibrin adhesive. This consists of 70–95 per cent human fibrinogen, 5–12 per cent cold insoluble globulin, factor XIII, aprotinin and platelet growth factor. Clotting is achieved by adding a thrombin and calcium chloride solution which is stored in a second syringe and mixed in a double-tube dispenser immediately before application[53]. Experimental anastomoses with fibrin glue alone have been performed in pig ileum and dog colon. Bursting strengths performed at 7 days in both groups showed no difference between the fibrin anastomoses, sutured anastomoses or adjacent bowel[54,55]. Work in rodents, however, has suggested that the glued anastomosis is weak during the critical lag period of healing[56] and thus clinical attempts to use fibrin glue as the sole method of anastomosis would seem unwise.

Laser welding. Initial experimental results from laser-constructed intestinal anastomoses appear promising[57,58]. Laser welding has already been used clinically in vasectomy reversal[59] and extraintracranial bypass[60]. The collagen substructure is altered by lasing, with interdigitation of individual fibrils, which is the basis of the tissue welding effect[61].

Preliminary work on laser closure of enterotomies in rodent ileum established a few basic principles[62–66]: carbon dioxide, NdYAG or argon lasers are all effective; optimum energy levels must be determined (too low and the wounds are weak, too high and charring occurs); non-contact lasers create stronger bonds; continuous laser delivery is preferred.

At optimum power levels, lased wound strength is equivalent or greater than in sutured enterotomies at all time-points[62,63,65,66]. Near-normal transmural histology is restored by 3 weeks, in marked contrast to sutured anastomoses[63]. Two early results of experimental laser-welded ileal anastomoses are now available[57,58]. In both reports a water-soluble intraluminal stent (PolySurge®; Laser Surge Incorporated, Rochester, New York, USA) was used to approximate the cut tissue edges. Lasing of the anastomotic seam was accomplished with a hand-held non-contact optical fibre. A continuous 5-watt wave of power was applied until tissue blanching and shrinkage was observed. Wound integrity, degree of tissue reaction and bursting pressures were comparable to standard sutured anastomoses, although laser-welded anastomoses appeared stronger between 1 and 2 weeks, with less inflammatory response. With the development of the biodegradable stent (PolySurge) and an automated laser delivery system (Exoscope; Laser Surge) which delivers laser energy uniformly to the anastomosis over 360°, many of the initial technical problems appear resolved. The encouraging reports should allow further experimental studies, culminating in a clinical trial.

Conclusions

The compression devices introduced in the past few years have produced initial clinical results comparable to those obtained with conventional sutured and stapled intestinal anastomoses. Numerous other theoretical advantages should ensure that these devices achieve more widespread usage. Indeed, many factors suggest that they will become the optimal way of establishing a mechanical anastomosis in the future. However, in addition to the natural caution of most surgeons, the major obstacle to this happening in the UK is the reluctance of the manufacturing companies to market these products in this country, despite their ready availability in the USA and continental Europe.

With currently available materials, glued anastomoses are not safe for clinical application. By contrast, the initial experimental reports of lased anastomoses appear highly promising and further research is warranted.

References

1. Amat C. Appareils à sutures: les viroles de Denans; les points de Bonnier; les boutons de Murphy. *Arch Med Pharmacie Militaires Paris* 1895; **25**: 273–85.
2. Murphy JB. Cholecysto-intestinal, gastro-intestinal, entero-intestinal anastomosis, and approximation without sutures. *Med Rec N Y* 1892; **42**: 665–76.
3. Senn N. Enterorrhaphy; its history, technique and present status. *JAMA* 1893; **21**: 215–35.
4. Boerema J. The technique of our method of transabdominal total gastrectomy in cases of gastric cancer. *Arch Chir Neerl* 1954; **6**: 95–111.
5. Irvin TT, Hunt TK. Reappraisal of the healing process of anastomosis of the colon. *Surg Gynecol Obstet* 1974; **138**: 741–6.
6. Herrmann JB, Woodward SC, Pulaski EJ. Healing of colonic anastomoses in the rat. *Surg Gynecol Obstet* 1964; **119**: 269–75.
7. Ordman LJ, Gillman T. Studies in the healing of cutaneous wounds. II. The healing of epidermal, appendageal and dermal injuries inflicted by suture needles and by the suture material in the skin of pigs. *Arch Surg* 1966; **93**: 883–910.
8. Lord MG, Broughton AC, Williams HT. A morphologic study on the effect of suturing the submucosa of the large intestine. *Surg Gynecol Obstet* 1978; **146**: 211–16.
9. Masden ET. An experimental and clinical evaluation of surgical suture material. *Surg Gynecol Obstet* 1953; **97**: 73–80.
10. Postlethwait RW. Long term comparative study of non-absorbable sutures. *Ann Surg* 1970; **171**: 892–8.
11. Postlethwait RW, Schauble JF, Dillon ML, Morgan J. Wound healing – II, an evaluation of surgical suture material. *Surg Gynecol Obstet* 1959; **108**: 555–66.
12. Getzen LC, Holloway CK. Comparative study of intestinal anastomotic healing in inverted and everted closures. *Surg Gynecol Obstet* 1966; **123**: 1219–27.
13. Letwin E, Williams HT, Harrison RC. The experimental healing of soft tissues. *J R Coll Surg Edinb* 1966; **12**: 121–33.
14. Forrester JC, Zederfeldt BH, Hayes TL, Hunt TK. Tape-closed and sutured wounds: a comparison by tensiometry and scanning electron microscopy. *Br J Surg* 1970; **57**: 729–37.
15. Golden T, Levy AH, O'Connor WT. Primary healing of skin wounds and incisions with a threadless suture. *Am J Surg* 1962; **104**: 603–12.
16. McGeehan D, Hunt D, Chaudhuri A, Rutter P. An experimental study of the relationship between synergistic wound sepsis and suture materials. *Br J Surg* 1980; **67**: 636–8.
17. Katz S, Izhar M, Mirelman D. Bacterial adherence to surgical sutures. A possible factor in suture induced infection. *Ann Surg* 1981; **194**: 35–41.
18. Matheson NA, Irving AD. Single layer anastomosis after rectosigmoid resection. *Br J Surg* 1975; **62**: 239–42.
19. Vink M. Local recurrence of cancer in the large bowel: the role of implantation metastases and bowel disinfection. *Br J Surg* 1954; **41**: 431–3.
20. Haverback CZ, Smith RR. Transplantation of tumour by suture thread and its prevention. An experimental study. *Cancer* 1959; **12**: 1029–42.
21. Cohn I. Implantation in cancer of the colon. *Surg Gynecol Obstet* 1967; **124**: 501–8.
22. Yu SK, Cohn I. Tumour implantation on colonic mucosa. *Arch Surg* 1968; **96**: 956–8.
23. O'Dwyer P, Ravikumar TS, Steele G. Serum dependent variability in the adherence of tumour cells to surgical sutures. *Br J Surg* 1985; **72**: 466–9.
24. McGregor JR, Galloway DJ, McCullough, George WD. Anastomotic suture materials and implantation metastases: an experimental study. *Br J Surg* 1989; **76**: 331–4.
25. Rubio CA, Nylander G. Surgical resection of the rat colon: effects on carcinogenesis by 1,2-dimethylhydrazine. *J Natl Cancer Inst* 1982; **68**: 813–15.
26. Williamson RC, Davies PW, Bristol JB, Wells M. Intestinal adaptation and experimental carcinogenesis after partial colectomy. Increased tumour yields are confined to the anastomosis. *Gut* 1982; **23**: 316–25.
27. Rubio CA, Nylander G, Wallin B, Sveander M, Alun ML, Duvander A. Partial colon resection as a promotor of cancer growth in the rat. *J Surg Oncol* 1984; **27**: 236–8.
28. Roe R, Fermor B, Williamson RC. Proliferative instability and experimental carcinogenesis at colonic anastomoses. *Gut* 1987; **28**: 808–15.
29. Phillips RK, Cook HT. Effect of steel wire sutures on the incidence of chemically induced rodent colonic tumours. *Br J Surg* 1986; **73**: 671–4.
30. McGregor JR, Galloway DJ, Jarrett F, George WD. Anastomotic materials and colorectal carcinogenesis. *Br J Surg* 1988; **75**: 603 (Abstract).
31. Hardy TG Jr, Pace WG, Maney JW, Katz AR, Kaganov AL. A biofragmentable ring for sutureless bowel anastomosis. An experimental study. *Dis Colon Rectum* 1985; **28**: 484–90.
32. Maney JW, Katz AR, Li LK, Pace WG, Hardy TG. Biofragmentable bowel anastomosis ring: comparative efficacy studies in dogs. *Surgery* 1988; **103**: 56–62.
33. Dyess DL, Curreri PW, Ferrara JJ. A new technique for sutureless intestinal anastomosis. A prospective, randomized, clinical trial. *Am Surg* 1990; **56**: 71–5.
34. Cahill CJ, Betzler M, Gruwez JA, Jeekel J, Patel JC, Zederfeldt B. Sutureless large bowel anastomosis: European experience with the biofragmentable anastomosis ring. *Br J Surg* 1989; **76**: 334–7.
35. Corman ML, Prager ED, Hardy TG Jr, Bubrick MP. Comparison of the Valtrac biofragmentable anastomosis ring with conventional suture and stapled anastomosis in colon surgery. Results of a prospective, randomized clinical trial. *Dis Colon Rectum* 1989; **32**: 183–7.
36. Hardy TG Jr, Aguilar PS, Stewart WR *et al.* Initial clinical experience with a biofragmentable ring for sutureless bowel anastomosis. *Dis Colon Rectum* 1987; **30**: 55–61.
37. Gross E, Eigler FW. Sutureless compression anastomosis of the distal colon and rectum. An expanded report of experiences with a total of 140 patients. *Chirurgie* 1989; **60**: 589–93.
38. Eigler FW, Gross E. Mechanical compression anastomosis (AKA-2) of the colon and rectum. Results of a prospective clinical study. *Chirurgie* 1986; **57**: 230–5.
39. Rosati R, Rebuffat C, Pezzuoli G. A new mechanical device for circular compression anastomosis. Preliminary results of animal and clinical experimentation. *Ann Surg* 1988; **207**: 245–52.
40. Malthaner RA, Hakki RZ, Saini N, Andrews BL, Harmon JW. Anastomotic compression button: a new mechanical device for sutureless bowel anastomosis. *Dis Colon Rectum* 1990; **33**: 291–7.
41. Jansen A, Keeman JN, Davies GA, Klopper PJ. Early experiences with magnetic rings in resection of the distal colon. *Neth J Surg* 1980; **32**: 20–7.
42. Jansen A, Brummelkamp WH, Davies GA, Klopper PJ, Keeman JN. Clinical applications of magnetic rings in colorectal anastomosis. *Surg Gynecol Obstet* 1981; **153**: 537–45.
43. Linn BS, Cecil F, Conly P, Canaday WR Jr, Wolcott MW. Intestinal anastomosis by invagination and gluing. *Am J Surg* 1966; **111**: 197–9.
44. Inou T. Studies on the surgical use of plastic adhesive. *Am J Proctol* 1962; **13**: 219–26.
45. O'Neill P, Healey JE, Clark RL, Gallager HS. Nonsuture intestinal anastomosis. *Am J Surg* 1962; **104**: 761–7.
46. Weilbaecher DA, Mathieu FJ, Cohn I. Nonsuture intestinal anastomosis. *Am J Surg* 1964; **107**: 353–60.
47. Stone HH. Nonsuture closure of cutaneous lacerations, skin grafting and bowel anastomosis. *Am Surg* 1964; **30**: 177–81.
48. Gennaro AR, Moreira CA Nonsuture colonic anastomosis. *Dis Colon Rectum* 1976; **19**: 245–9.
49. Woodward SC, Herrmann JB, Cameron JL, Brandes G, Pulsaski EJ, Leonard F. Histotoxicity of cyanoacrylate tissue adhesive in the rat. *Ann Surg* 1965; **162**: 113–22.
50. Matsumoto T, Pani KC, Kovaric JJ, Hamit HF. Tissue adhesive in intestinal surgery. *Am Surg* 1969; **35**: 210–17.
51. Kirkegaard P, Christensen AB, Ibsen J, Hegedus V, Christiansen J. Experimental nonsuture colonic anastomoses. *Am J Surg* 1980; **139**: 233–6.
52. Stirling CT, Cohn I. Nonsuture small bowel anastomosis. Experimental study with cyanoacrylate monomer. *Am Surg* 1965; **31**: 587–9.
53. Petrelli NJ, Cohen H, DeRisi D, Ambrus JL, Williams P. The application of tissue adhesives in small bowel anastomoses. *J Surg Oncol* 1982; **19**: 59–61.
54. Kjaergaard J, Nordkild P, Sjontoft E, Hjortrup A. Non-sutured fibrin adhesive vs. sutured anastomosis. A comparative intra-individual study in dog colon. *Acta Chir Scand* 1987; **153**: 599–601.

55. Hjortrup A, Nordkild P, Kiaergaard J, Sjontoft E, Olesen HP. Fibrin adhesive *versus* sutured anastomosis: a comparative intraindividual study in the small intestine of pigs. *Br J Surg* 1986; **73**: 760–1.
56. Haukipuro KA, Hulkko OA, Alavaikko MJ, Laitinen ST. Sutureless colon anastomosis with fibrin glue in the rat. *Dis Colon Rectum* 1988; **31**: 601–4.
57. Costello AJ, Johnson DE, Cromeens DM, Wishnow KI, von Eschenbach AC, Ro JY. Sutureless end-to-end bowel anastomosis using Nd:YAG and water-soluble intraluminal stent. *Lasers Surg Med* 1990; **10**: 179–84.
58. Sauer JS, Hinshaw JR, McGuire KP. The first sutureless, laser-welded, end-to-end bowel anastomosis. *Lasers Surg Med* 1989; **9**: 70–3.
59. Jarow R, Cooley BC, Marshall FF. Laser-assisted vasal anastomosis in the rat and man. *J Urol* 1986; **36**: 1132–5.
60. Jain KK. Sutureless extra-intracranial anastomosis by laser. *Lancet* 1984; **ii**: 816–17.
61. Schober R, Ulrich F, Sander T, Durselen H, Hessel S. Laser-induced alteration of collagen substructure allows microsurgical tissue welding. *Science* 1986; **232**: 1421–2.
62. Mercer CD, Minich P, Pauli B. Sutureless bowel anastomosis using Nd:YAG laser. *Lasers Surg Med* 1987; **7**: 503–6.
63. Cespanyi E, White RA, Lyons R *et al.* Preliminary report: a new technique of enterotomy closure using Nd:YAG laser welding compared to suture repair. *J Surg Res* 1987; **42**: 147–52.
64. Lim KH, Wang S, Kaplan P, Rose DM, Cunningham JN. Factors that affect bursting strength of intestinal anastomosis with CO_2 laser. *Lasers Surg Med* 1986; **6**: 202 (Abstract).
65. Vlasak J, Kopchok G, White R. Closure of rabbit ileum enterotomies with the argon and CO_2 lasers – bursting pressures and histology. *Lasers Surg Med* 1988; **8**: 162 (Abstract).
66. Sauer JS, Rogers DW, Hinshaw JR. Bursting pressures of CO_2 laser-welded rabbit ileum. *Lasers Surg Med* 1986; **6**: 106–9.
67. McCue JL, Sheffield JP, Uff CR, Phillips RK. Anastomotic cancer: do sutures matter? *Gut* 1991; (in press) (Abstract).

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Announcement

European Surgical Fellowships

Since 1990, the Council of *The British Journal of Surgery* has awarded European Fellowships, each holding a value of up to £3000. The first four successful applicants have now completed their Fellowships and Council has been pleased with the development of the scheme to date.

Mr R. Graeme Wilson used the opportunity to visit European centres developing laparoscopic techniques. Mr A. Ross Naylor used the opportunity to visit various vascular centres in Europe with particular reference to carotid artery surgery. Mr Ashley Dennison used the opportunity to visit a specialist hepatobiliary unit in Switzerland. Mr Colin D. Johnson took the opportunity to visit centres in Germany with a special interest in hepatobiliary and pancreatic surgery.

Three Fellowships have been awarded for 1991 to Mr B. J. Jenkins (London), Mr T. A. Lees (Newcastle-upon-Tyne) and Mr I. D. Anderson (Manchester).

Council are anxious to expand the scheme to allow surgeons working in other European countries to visit the UK. It is hoped that the candidates will use the Fellowships to visit surgical centres of their choice to extend their surgical experience. Fellowships will not be awarded solely for the purpose of attending courses or meetings.

It is Council's intention to offer European Fellowships once again in 1992. Applicants should submit details of their proposed itinerary and its anticipated costs, together with a curriculum vitae and two letters of support from senior colleagues. They should explain briefly how such a visit might broaden their experience and assist their career. Applications should be sent to the Company Secretary, Professor D. C. Carter, University Department of Surgery, Royal Infirmary, Edinburgh EH3 9YW by 31 January 1992.

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Recurrence of colorectal cancer after sutured and stapled large bowel anastomoses

The purpose of this study was to compare surgical stapling and manual suturing techniques with respect to the incidence of tumour recurrence in patients with colorectal cancer: 294 patients undergoing potentially curative resections for colorectal cancer were randomly allocated to receive sutured (n = *142*) *or stapled* (n = *152*) *anastomoses. The mean(s.e.m.) incidence of tumour recurrence at the end of 24 months was 29·4(4·4) per cent in the sutured group, compared with 19·1(3·9) per cent in the stapled group* ($P<0{\cdot}05$)*. The corresponding rates for cancer-specific mortality at 24 months were 22·3(4·1) per cent and 10·9(3·0) per cent respectively* ($P<0{\cdot}01$)*. A multiple regression analysis revealed that the influence of anastomotic technique on recurrence and mortality rate was independent of tumour stage. These results suggest that in colorectal cancer surgery the use of stapling instruments for anastomotic construction could be associated with a reduction in the incidence of recurrence and mortality rate by as much as 50 per cent.*

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The use of surgical stapling instruments following large bowel resection for malignant disease has recently been questioned. The concern regarding the safety of stapled restorative resections was based on several reviews reporting recurrence rates of 20–32 per cent following potentially curative resections for rectal cancer[1–5]. Other investigators, however, have failed to identify an adverse effect associated with stapling[6–9]. Previous reports investigating the potential influence of stapling techniques on the long-term outcome of patients with colorectal cancer have been based on retrospective and often small patient series. The present study was undertaken to determine the relative frequency of recurrence and disease-free survival rates in a prospectively studied group of patients who underwent resection for colorectal cancer and who were randomized to receive either sutured or stapled anastomoses.

Patients and methods

All patients in this study have been subjects of a previously reported prospective controlled trial comparing anastomotic leakage after manual suturing and surgical stapling techniques[10]. The study population was selected from 463 consecutive patients who underwent surgery for colorectal cancer between April 1985 and April 1989 under the care of 13 surgeons in five hospitals in Scotland. The anastomotic technique used in these patients was determined by randomization at the time of surgery. Randomization was performed after the resection had taken place and only after the surgeon was satisfied that both suturing and stapling techniques were feasible and equally appropriate. On 33 occasions the use of one or the other technique was considered inappropriate and randomization was not performed – these patients were excluded from further analysis. A stratified randomization method was used whereby each surgeon contributed equal numbers of sutured and stapled cases into the study. All patients eligible for study under the care of the participating consultants were included in the trial irrespective of the grade of the operating surgeon. Most of the operations were performed or directly supervised by consultant surgeons (81 per cent in the sutured and 83 per cent in the stapled group). The use of routine intraoperative bowel washouts was not specified by the study protocol. As a result of the stratified randomization method, those participants who routinely used bowel washouts applied this technique in equal numbers of sutured and stapled patients.

Ninety-six patients (22·3 per cent) underwent palliative resections and were excluded from further analysis. Of the remaining 334 patients who had potentially curative resections, 12 (3·6 per cent) died within 30 days of surgery and follow-up data were incomplete in 28 (8·4 per cent) patients. The remaining 294 patients constituted the study group.

Sutured colocolic and colorectal anastomoses were carried out using a single layer of interrupted 2/0 polyamide (Nurolon®, Ethicon Ltd., Edinburgh, UK) suture material. Ileocolic anastomoses were performed in either the same fashion or in two layers using an inner layer of continuous 2/0 polyglycolic acid (Dexon® Plus, Davis and Geck, Gosport, UK) and an outer layer of 2/0 polyamide. All colorectal stapled anastomoses were performed with the TA®, GIA® or EEA® series of surgical stapling instruments (Auto Suture UK, Ascot, UK).

The tumour nodes metastasis (TNM) classification[11] was used for tumour staging. Staging was done after surgical exploration of the abdomen and pathological examination of the resected specimens. The stage groupings used are shown in *Table 1*. Curative surgery was defined as removal of all macroscopically evident disease at the time of surgery with tumour-free resection margins on histological examination. Two patients, both with stapled anastomoses, who had excision of solitary liver metastases at the time of resection of the primary tumour were considered as having had a curative operation. The method of follow-up for patients in the study was left to the discretion of the individual consultants. The only condition imposed by the study protocol for follow-up was that the anastomosis be visualized at least once a year, usually by flexible sigmoidoscopy or colonoscopy, or occasionally by double contrast barium enema. Deaths occurring within 30 days of the surgical procedure were considered as operative mortality. Local recurrence was defined as clinical, histological or post-mortem evidence of recurrent carcinoma at or in the region of the anastomosis. In most cases it was not possible to differentiate between anastomotic and perianastomotic recurrence. Patients who developed tumour spread to other intra-abdominal sites, lung, liver and bones during follow-up were classified as distant recurrences.

Disease-free interval and survival was measured from the time of resection. The estimation of the cumulative probability of recurrence and cancer-specific mortality rates were performed by the life-table method of Kaplan and Meier[12]. Comparison of recurrence and cancer-specific mortality rates between the sutured and stapled groups was done by log rank test. Cox's proportional hazards regression model

Table 1 *Tumour stage related to the TNM classification*

Stage 0	T_{is}	N_0	M_0
Stage I	T_1, T_2	N_0	M_0
Stage II	T_3, T_4	N_0	M_0
Stage III	Any T	N_1, N_2, N_3	M_0
Stage IV	Any T	Any N	M_1

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was used for multivariate adjustment for the influence of covariates on recurrence and mortality rates simultaneously[13].

Results

The study population consisted of 142 patients with sutured and 152 patients with stapled anastomoses. Patient characteristics for the sutured and stapled groups are outlined in *Table 2*.

Forty-five patients in the sutured group (31·7 per cent) and 48 patients in the stapled group (31·6 per cent) received perioperative blood transfusions (during the same admission when surgical resection was performed). Of the total study population, 109 had restorative rectal excisions for carcinoma of the rectum or rectosigmoid and 112 had right hemicolectomy and ileocolic anastomosis for right-sided colonic tumours. The remaining 73 patients had segmental bowel resections and colocolic anastomoses. The distribution of anastomotic sites in the sutured and stapled groups is shown in *Table 3*.

Table 4 illustrates the stage and grade of the tumours for the patients in the two groups. Follow-up for the patients was 11–54 months. The median follow-up was 21·0 months in the sutured group and 21·2 months in the stapled group.

The cumulative probability of tumour recurrence is illustrated in *Figure 1*, expressed as the proportion of recurrence-free patients plotted against time during the follow-up period. The incidence of tumour recurrence in patients with sutured anastomoses was significantly higher than for those with stapled anastomoses ($P<0·05$). Of the patients in the sutured group 29·4(4·4) per cent had recurrence diagnosed by the end of the second postoperative year compared with 19·1(3·9) per cent in the stapled group.

Table 2 *Patient characteristics*

	Sutures ($n=142$)	Staples ($n=152$)
Sex ratio (M:F)	69:73	69:83
Age (years)	69·6(11·3)	68·7(11·3)
Weight (kg)	62·5(12·7)	63·7(10·8)
Height (cm)	165·2(10·2)	164·9(8·3)
Haemoglobin (g/dl)	12·7(2·1)	12·8(2·0)
WBC ($\times 10^9$/l)	8·4(2·9)	8·4(2·6)
Albumin (g/l)	37·7(5·1)	38·5(4·6)
Operating time (min)	119·8(40·9)	103·3(41·6)

Values are mean(s.d.). WBC, white blood cell count

Table 3 *Anastomotic site*

Anastomoses	Sutures ($n=142$)	Staples ($n=152$)
Colorectal	52	57
Colocolic	39	34
Ileocolic	51	61

Table 4 *Tumour stage and grade*

	Sutures ($n=142$)	Staples ($n=152$)
Tumour stage		
Stage I	15	20
Stage II	76	88
Stage III	51	42
Stage IV	0	2
Tumour grade		
GX (Cannot be assessed)	5	6
G1 (Well differentiated)	8	23
G2 (Moderately differentiated)	101	105
G3/G4 (Poorly differentiated)	28	18

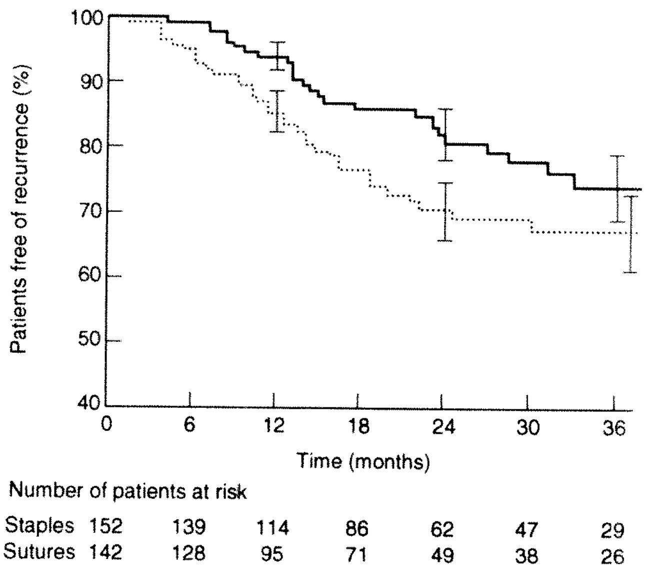

Figure 1 *The incidence of tumour recurrence in the sutured (-----) and stapled (——) groups expressed as a life-table curve*

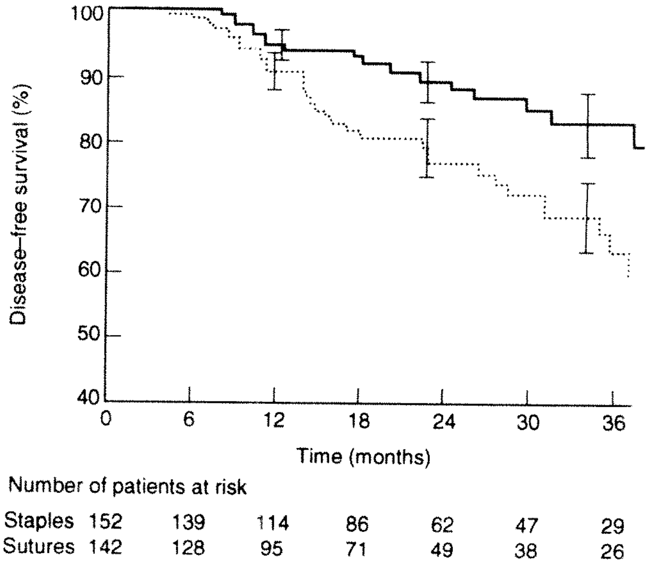

Figure 2 *Cancer-specific mortality rates in the sutured (-----) and stapled (——) groups expressed as a life-table curve*

Figure 2 illustrates the cumulative probability of cancer-specific death in the two groups. The higher incidence of tumour recurrence in the sutured group was paralleled by a significantly higher cancer-specific mortality rate ($P<0·01$). By the end of 24 months, 22·3(4·1) per cent of the patients with sutured anastomoses had died as a result of cancer compared with 10·9(3·0) per cent in the stapled group.

The number and site of recurrences in each group is related to tumour stage in *Table 5*.

In order to identify and adjust for the influence of all the covariates that were associated with the outcome, Cox's regression analysis was used. Only tumour stage and anastomotic technique were seen to be significantly associated with recurrence (*Table 6*). A higher incidence of recurrence was seen in men, but with a borderline significance. The difference between sutured and stapled groups in terms of recurrence rate was statistically significant ($P<0·05$) after correction for tumour stage in the multiple regression model.

The 'relative hazard' of recurrence in the stapled group relative to the sutured group was 0·58 (95 per cent confidence interval 0·35–0·97); there was a 42 per cent reduction in the

Table 5 *Number and site of recurrences in sutured and stapled groups tabulated by tumour stage*

	Recurrent tumour			
	Local	Local distant	Distant	All recurrences
Sutured group				
Stage I (15)	2	0	0	2
Stage II (76)	7	7	4	18
Stage III (51)	7	8	2	17
Total (142)	16	15	6	37
Stapled group				
Stage I (20)	0	0	1	1
Stage II (88)	6	6	2	14
Stage III (42)	4	1	5	10
Stage IV (2)	1	0	0	1
Total (152)	11	7	8	26

Table 6 *Association between tumour recurrence and perioperative variables (Cox's regression analysis)*

Variable	Regression coefficient	Standard error	*P*
Age			0·60
Sex			0·051
Stage	0·683	0·218	0·001
Grade			0·38
Haemoglobin			0·75
Albumin			0·53
Transfusion			0·93
Anastomotic technique	−0·546	0·263	0·035
Anastomotic site			0·71

Table 7 *Association between cancer-specific mortality and perioperative variables (Cox's regression analysis)*

Variables	Regression coefficient	Standard error	*P*
Age			0·18
Sex			0·06
Stage	0·952	0·249	0·0001
Grade			0·34
Haemoglobin			0·73
Albumin			0·59
Transfusion			0·72
Anastomotic technique	−0·695	0·294	0·015
Anastomotic site			0·75

incidence of tumour recurrence associated with the use of stapling instruments (95 per cent confidence interval 3–65 per cent).

Univariate analysis with regard to disease-free survival revealed that tumour stage, grade, anastomotic technique and sex had statistically significant associations with the cancer-specific mortality rate. In the multiple regession model, sex and tumour grade no longer remained significant independent predictors of poorer disease-free survival. However, the significantly higher cancer-specific mortality rate for patients with sutured anastomoses remained unaltered after correcting for tumour stage (*Table 7*).

The 'relative hazard' of cancer-specific mortality (stapled *versus* sutured) was 0·5 (95 per cent confidence interval 0·28–0·89); the cancer-specific mortality rate in the stapled group was 50 per cent of that in the sutured group (95 per cent confidence interval 11–72 per cent).

Discussion

Previous studies on patients with colorectal cancer have shown either a poor outcome associated with the use of stapling techniques or no difference between patients with sutured and stapled anastomoses in terms of recurrence rates. In contrast, this study has identified a significant reduction in the incidence of tumour recurrence and cancer-specific mortality rate when stapling instruments were used for anastomotic construction compared with conventional manual suturing techniques in colorectal cancer surgery.

High incidences of tumour recurrence in patients with stapled anastomoses have only been reported following restorative resections for rectal carcinoma[1–4], suggesting that the increasing use of stapling instruments has resulted in an inappropriate abandonment of abdominoperineal resection in favour of restorative resections in the management of rectal cancer. Surgical staplers have probably accelerated the rate with which sphincter-saving procedures were adopted, although the retreat from total rectal excisions towards sphincter saving operations was well underway before the introduction of the circular stapling instruments[14–16].

It has been suggested that stapling instruments may allow a colorectal anastomosis to be performed at a lower level than would be possible by suturing techniques[17,18]. Conceivably, the effort to perform a low stapled anastomosis in such cases might lead to a compromise in the extent of tumour clearance. Anderberg *et al.*[2] have put forward this contention as a potential mechanism by which stapling techniques could adversely affect recurrence rates in patients with rectal cancer.

In theory, there are mechanisms other than compromised tumour clearance by which the anastomotic technique could have an influence on the prognosis of colorectal cancer: in this context the scraping of tumour cells by the intraluminal stapler gun and their deposition at the site of the anastomosis[5], increased intraluminal trauma predisposing to the implantation of exfoliated tumour cells[19], or delayed mucosal healing of stapled anastomoses[20] have been postulated as potential mechanisms by which stapling could have an adverse influence. The extent of resection for intraperitoneal large bowel tumours would not be expected to differ when either sutures or staplers are used for establishing recontinuity. Therefore, if any of the above mechanisms has an effect, it would be expected that the results with stapled reconstructions after resection of intraperitoneal colonic tumours would be worse than the results achieved by suturing. Of the reports in the literature comparing stapling and suturing techniques, only one has included colonic (intraperitoneal) tumours[9]. In that study survival, disease-free survival and recurrence rates were very similar after 856 sutured and 255 stapled colonic anastomoses.

This study is the only report where the influence of anastomotic technique on the outcome of colorectal cancer has been studied in randomized patient groups. In uncontrolled and non-randomized studies, it would be expected that anatomical considerations that encourage the use of staplers are also likely to be associated with a higher risk of tumour recurrence. The discordance between the results of the present study and other previous reports (all of which were retrospective and uncontrolled) could be explained by this 'patient selection' effect, which is likely to have biased the results of the previous studies. As would be anticipated from the randomized nature of the study, the sutured and stapled groups were well matched in terms of the recorded perioperative variables. Furthermore, we noted that the only significant determinants of recurrence or mortality rate were tumour stage and anastomotic technique, and the disease-free survival advantage in favour of the stapled group remained unchanged after correcting for tumour stage. Nevertheless, the study population represented a subgroup selected from a larger cohort of patients. In this respect, the approach fell short of a prospective randomized evaluation of stapling and suturing techniques specifically designed to compare them in relation to the outcome of colorectal cancer.

As well as anastomotic technique, anastomotic materials have been implicated as a potential influence on local tumour recurrence. Studies in rodents with chemical carcinogens have shown that stainless steel implanted in the bowel could be either more or less potent as a promoter than braided suture materials, depending on the time of carcinogen administration in relation to surgery[21-23]. O'Dwyer *et al.*[24] and McGregor *et al.*[25] have demonstrated with *in vitro* assays that tumour cells adhere in significantly greater numbers to polyamide or polyglycolic acid than to stainless steel and that stainless steel transfers significantly fewer intraluminal cells compared with braided suture materials in animal models.

All sutured anastomoses in these patients were constructed using braided polyamide and/or polyglycolic acid. Differing properties of stainless steel and braided suture materials with respect to tumour cell entrapment or adherence may, at least in part, have been responsible for the poorer results observed in patients with sutured anastomoses in this study.

In previous reports we have demonstrated that sutured colorectal anastomoses have a higher incidence of radiological leaks compared with staples[10] and that clinical or subclinical anastomotic leaks might be associated with a higher incidence of tumour recurrence[26]. These observations raise the possibility that the influence of anastomotic leaks and anastomotic technique on tumour recurrence could be interrelated. In the current study the incidence of clinically evident anastomotic dehiscence was similar between the sutured and stapled groups. However, the radiological leak rates were not known for most patients since postoperative contrast radiography was not used routinely. It is therefore not possible to make a comment regarding the influence of leaks on the outcome.

In conclusion, these results suggest that the use of stapling instruments in colorectal cancer surgery could be associated with a reduction in the incidence of local recurrence and cancer-specific mortality rates by as much as 50 per cent. The mechanisms leading to this reduction in this study remain unclear; however, if they are confirmed by other studies, these observations are likely to have important clinical implications. Further studies are required to clarify the role of anastomotic techniques and materials on the long-term outcome of patients with colorectal cancer.

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References

1. Hurst PA, Prout WG, Kelly JM, Bannister JJ, Walker RT. Local recurrence after low anterior resection using the staple gun. *Br J Surg* 1982; **69**: 275–6.
2. Anderberg B, Enblad P, Sjodahl R, Wetterfors J. Recurrent rectal carcinoma after anterior resection and rectal stapling. *Br J Surg* 1983; **70**: 1–4.
3. Reid JDS, Robins RE, Atkinson KG. Pelvic recurrence after anterior resection and EEA stapling anastomosis for potentially curable carcinoma of the rectum. *Am J Surg* 1984; **147**: 629–32.
4. Bisgaard C, Svanholm H, Jensen AS. Recurrent carcinoma after low anterior resection of the rectum using the EEA staple gun. *Acta Chir Scand* 1986; **152**: 157–60.
5. Rosen CB, Beart RW Jr, Ilstrup DM. Local recurrence of rectal carcinoma after hand-sewn and stapled anastomoses. *Dis Colon Rectum* 1985; **28**: 305–9.
6. Ohman U, Svenberg T. EEA stapler for mid-rectum carcinoma – review of recent literature and own initial experience. *Dis Colon Rectum* 1983; **26**: 775–84.
7. Ohman U. Curative potential of EEA stapler in rectal carcinoma. *Acta Chir Scand* 1986; **152**: 59–64.
8. Kennedy HL, Langevin JM, Goldberg SM *et al.* Recurrence following stapled coloproctostomy for carcinomas of the mid portion of the rectum. *Surg Gynecol Obstet* 1985; **160**: 513–16.
9. Wolmark N, Gordon PH, Fisher B *et al.* A comparison of stapled and hand sewn anastomoses in patients undergoing resection for Dukes' B and C colorectal cancer. An analysis of disease-free survival and survival from the NSABP prospective clinical trials. *Dis Colon Rectum* 1986; **29**: 344–50.
10. West of Scotland and Highland Anastomosis Study Group. Suturing or stapling in gastrointestinal surgery: a prospective randomized study. *Br J Surg* 1991; **78**: 337–41.
11. American Joint Committee on Cancer. *Manual for Staging of Cancer*. 3rd edn. Philadelphia: J. P. Lippincott, 1988: 1–24, 75–80.
12. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *Am Stat Assoc* 1958; **53**: 457–81.
13. Cox DR. Regression models and life tables. *J R Stat Soc [B]* 1972; **34**: 187–220.
14. Lockhart-Mummery HE, Ritchie JK, Hawley PR. The results of surgical treatment for carcinoma of the rectum at St. Mark's Hospital from 1948 to 1972. *Br J Surg* 1976; **63**: 673–7.
15. Jones PF and Thomson HJ. Long term results of a consistent policy of sphincter preservation in the treatment of carcinoma of the rectum. *Br J Surg* 1982; **69**: 564–8.
16. Williams NS. Rationale for preservation of the anal sphincter in patients with low rectal cancer. *Br J Surg* 1984; **71**: 575–81.
17. Goligher JC, Lee PWR, Macfie J, Simpkins KC, Lintott DJ. Experience with the Russian model 249 suture gun for anastomosis of the rectum. *Surg Gynecol Obstet* 1979; **148**: 517–24.
18. Heald RJ. Towards fewer colostomies – the impact of circular stapling devices on the surgery of rectal cancer in a district hospital. *Br J Surg* 1980; **67**: 198–200.
19. Norgen J, Svensson JO. Anal implantation metastasis from carcinoma of the sigmoid colon and rectum: a risk when performing anterior resection with the EEA stapler? *Br J Surg* 1985; **72**: 602.
20. Polglase AL, Hughes ESR, McDermott FT, Pihl E, Burke FR. A comparison of end-to-end staple and suture colorectal anastomosis in the dog. *Surg Gynecol Obstet* 1981; **152**: 792–6.
21. Phillips RKS, Cook HT. Effect of steel wire sutures on the incidence of chemically induced rodent colonic tumours. *Br J Surg* 1986; **73**: 671–4.
22. McGregor JR, Galloway DJ, Jarrett F, George WD. Anastomotic materials and colorectal carcinogenesis. *Br J Surg* 1988; **75**: 603.
23. Calderisi RN, Freeman HJ. Differential effects of surgical suture materials in 1,2-dimethylhydrazine induced rat intestinal neoplasia. *Cancer Res* 1984; **44**: 2827–30.
24. O'Dwyer P, Ravikumar TS, Steele G Jr. Serum dependent variability in the adherence of tumour cells to surgical sutures. *Br J Surg* 1985; **72**: 466–9.
25. McGregor JR, Galloway DJ, McCulloch P, George WD. Anastomotic suture materials and implantation metastasis: an experimental study. *Br J Surg* 1989; **76**: 331–4.
26. Akyol AM, Galloway DJ, Murray GD, McGregor JR, George WD. Anastomotic leaks and tumour recurrence. *Eur J Surg Oncol* 1991; **17**: 113–14.

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Abdominal injuries in the war wounded of Afghanistan: a report from the International Committee of the Red Cross Hospital in Kabul

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This report is from the hospital opened by the International Committee of the Red Cross, in Kabul, which receives acute war-wounded patients from the Afghanistan conflict. Of more than 1000 operations carried out by the New Zealand team in a 6-month period, there were 70 laparotomies for penetrating wounds. These injuries were dealt with by established surgical techniques. The main area of controversy was the management of colonic wounds where the recent trend away from mandatory colostomy was followed by good results. Selective primary repair was achieved in 16 of 27 patients with colonic injury with no mortality and minimal morbidity. The right colon was considered particularly favourable for primary anastomosis. The overall mortality rate for all laparotomies was 13 per cent, with injuries to the liver, major veins and rectum particularly being fatal. There were eight negative laparotomies.

As part of the International Committee of the Red Cross (ICRC) mandate to provide assistance and protection to civilians in war conflict areas, the ICRC has set up surgical hospitals on the border of Afghanistan (Peshawar, Quetta) and now in Kabul, the capital of Afghanistan. The hospitals in Peshawar and Quetta were established in 1981 and 1983, respectively, at a time when ICRC was denied access to the war zone itself. In October 1988 the ICRC Hospital for War Wounded was finally opened in Kabul.

The Russian army left Afghanistan in February 1989, after a 9-year occupation. The conflict continues with the political situation degenerating into civil war, and Kabul remains in the front line, a city under siege with rocket attacks a daily occurrence.

The New Zealand Red Cross Society sent a surgical team to work in the ICRC hospital in Kabul from September 1989 to March 1990. This team comprised one surgeon, one anaesthetist, and one theatre nurse; the medical personnel worked for a maximum of 3 months each. The workload was shared with a second surgical team from another National Red Cross Society.

There were ten expatriate Red Cross nurses, assisted by 70 lay assistants from the local Afghan community. Facilities included plain radiography, minimal laboratory service of haematocrit but no electrolyte estimation and limited availability of blood; there was no ventilatory equipment.

The hospital opened with a planned occupancy of 50 beds. However, during the period of reporting the bed occupancy ranged between 100 and 160. In all, 650 admissions came under the care of the New Zealand team, requiring more than 1000 operations covering the full range of war surgery: compound fractures, amputations, wound debridement, delayed primary closure, craniotomies, chest injuries, laparotomies and burns.

This is a report on the 70 laparotomies performed by the New Zealand surgical team during this 6-month period.

Patients and methods

Seventy patients requiring laparotomy were admitted from the first week in September 1989 to March 1990. All wounds were penetrating, 92 per cent from shell fragments from exploding rockets or mines and 8 per cent from gunshot. There were no stabbing injuries, and no blunt abdominal trauma. Small bowel, large bowel, liver and stomach were the organs most commonly injured, with a similar case distribution to those of World War II and Vietnam[1] (*Table 1*). About half of the patients had more than one organ system injured (*Table 2*). Two-thirds (48) arrived within 12 h of injury; the remainder (22) arrived 1–4 days later.

Admissions requiring laparotomy were usually one or two a day; if greater, the second surgical team assisted so that there was no delay in management. Fifty per cent of the laparotomies were done on patients under the age of 14 years. On arrival at hospital all patients were resuscitated with intravenous fluids, and anti-tetanus serum, tetanus toxoid and antibiotics were given. Investigations included chest and abdominal anteroposterior and lateral radiography, haematocrit and

Table 1 *Laparotomies: distribution of 114 injured organs in 70 patients*

	No. of injuries
Stomach	10
Small intestine	33
Colon and rectum	35
Liver	17
Spleen	1
Kidney	5
Bladder	3
Pancreas	0
Great vessels	3
Gallbladder	1
Ureter	1
Diaphragm	5
No injury (exploration only)	8

Table 2 *Number of organ systems injured per patient*

No. of organ systems injured	No. of patients	No. of deaths
1	29	2
2	15	2
3	11	4
4	5	1
5	1	0
6	1	0
0	8	0

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blood grouping. The antibiotics used were metronidazole, gentamicin and ampicillin, which were continued routinely for 5 days.

General anaesthesia with endotracheal intubation and muscle relaxation was used, and a nasogastric tube and urinary catheter were inserted. Midline incisions were used with closure of the linea alba using polyglactin sutures, and polypropylene sutures for skin closure. All stomach, small and large bowel repairs were performed with two layers of polyglactin suture. Full lavage with saline was carried out to all parts of the abdominal cavity. Drains, either Penrose or suction, were frequently used. The entry and exit wounds were fully debrided and left open to close slowly by granulation. Occasionally, delayed primary suture of small wounds was carried out on the fifth to seventh day under local anaesthesia. Patients were nursed after operation in a special care area, and remained under the care of the operating surgeon. Full records were kept of their clinical progess until discharge from hospital.

Results

The management of specific intra-abdominal injuries was as follows.

Stomach

There were ten injuries to the stomach, and these were never isolated, being associated with diaphragmatic, liver, small bowel or colonic perforations. All stomach perforations were treated with two-layer continuous closure. No gastric resection was required. There were no complications.

Small intestine

There were 33 patients with small bowel perforations, ranging from simple through and through, or a series of sequential perforations, to complete disruption with involvement of the adjacent mesentery. Twenty-two patients had injuries of other organs: in 17 cases the organ was the colon or rectum. Treatment procedures were individual suture repair, or resection of the involved segment and anastomosis, or a combination of these two procedures. There were no complications in the series.

Colon

Twenty-seven patients had injury to the colon; 18 of these had injuries to other organs as well, two with a second colonic injury to another separate area, e.g. ascending and sigmoid colon. Colon injuries were managed by: (1) primary repair with return to the peritoneal cavity; (2) resection and primary anastomosis; (3) exteriorization of the injured part as a loop colostomy; or (4) resection and double-barrelled colostomy (Paul Mikulicz procedure). Primary suture with exteriorization of the repaired segment[2] was not performed. These injuries are considered below with regard to their anatomical distribution.

Of the eight ascending colon injuries, one was treated by primary suture (for a small perforation). The remaining seven had severe disruptive injury, with marked intraperitoneal contamination. They were managed by resection, six with immediate ileocolic anastomosis. The one other, which was 4 days old with severe contamination, was managed with resection, proximal ileostomy and distal mucous fistula. All patients survived with no complications, and closure of the ileostomy was carried out 3 months later.

There were ten injuries to the transverse colon. Two minor injuries were repaired by primary suture. Two severe injuries of the proximal part were managed by extended right hemicolectomy and anastomosis. The six other perforations of the transverse colon comprised four treated by exteriorization as a loop colostomy, and two which required resection and a double-barrelled colostomy.

There were 11 patients with perforating injuries of the descending and sigmoid colon. Five patients who had small perforations, less than 25 per cent of the colonic circumference, were managed by primary suture. There was only minor contamination in these cases. The other six perforated colons were brought out as loop colostomies at the site of injury. Resection and anastomosis was not carried out.

Therefore, 16 of the 29 colonic injuries were treated by primary repair. After operation there was no indication of ongoing intraperitoneal sepsis, no abscess formation and no fistula. There were no deaths from this management of colon wounds.

Rectum

There were six patients with rectal injury from penetrating buttock or perineal wounds, three of whom had associated injuries, two to the bladder and one to the small bowel. The surgical management for all patients was: (1) defunctioning proximal colostomy; (2) suture repair of the rectal injury, if possible; (3) distal rectal irrigation; and (4) presacral drainage. In two of these cases no suture repair was possible owing to the severe disruption of the distal rectum. There were two deaths; one patient had a major disruption of the rectum presenting 12 h after injury, and the second young man arrived 3 days after injury. Both patients remained septicaemic and one had renal failure; both died within 12 h of surgery.

Liver

The range of injury in 17 patients was from minor non-bleeding lacerations to severe liver trauma. Five patients required no surgical intervention, seven were managed by debridement and suture, three by debridement and omental pack, and two exsanguinated during surgery from extensive parenchymal disruption.

Other visceral injuries

One case of penetrating injury to the gallbladder was managed by cholecystectomy, and the only patient with splenic rupture was treated by splenectomy. There were no cases of duodenal or pancreatic injury.

Genitourinary

There were five patients with kidney injury, one of whom required a lower pole partial nephrectomy; otherwise these injuries were treated conservatively. One ureteric injury was managed by primary repair. Three patients with bladder perforation had closure and catheter drainage. One patient with a posterior urethral injury was managed by railroading catheters, leaving urethral and suprapubic catheters in place, suturing down the prostate to the perineum, and paravesical drainage.

Vascular

There were three patients with major vascular injury, all presenting with marked hypovolaemia and other organ injury. In a 5-year-old boy the inferior mesenteric vessels required ligation, and he survived despite colon, liver, stomach and diaphragmatic injuries. The other two patients died from severe injury to the great vessels, one from disruption of the junction of the superior mesenteric and portal vein, the other from combined injury of the common iliac vein and internal iliac vein and artery.

Diaphragm

Travelling missiles may pass through both thorax and abdomen via the diaphragm. Five such injuries were handled by chest tubes for the pneumohaemothorax, suture repair to the diaphragm, and separate midline laparotomy to attend to the intraperitoneal injury. Marked rice contamination of the intrapleural cavity from a stomach perforation was a finding in three cases, but lavage and appropriate drainage prevented any subsequent problem. Spleen, liver, small bowel and large bowel were other organs involved in associated injuries.

No injury

In eight cases with suspected intra-abdominal trauma, no injury was found other than trauma to the anterior abdominal wall

Table 3 *Mortality: injuries, time factor and causes of death*

Patient no.	Sex	Age (years)	Injuries	Time from injury to surgery	Time from surgery till death	Cause of death
1	M	10	Liver (major), pneumothorax, diaphragm, small bowel, colon	0·5 h	During surgery	Exsanguination
2	M	35	Liver (major)	0·5 h	1 h	Exsanguination
3	M	55	Liver (major)	24 h	During surgery	Exsanguination
4	F	6	Portal vein, superior mesenteric vein, stomach, jejunum	0·5 h	1 h	Exsanguination
5	M	10	Iliac veins and artery, small bowel, right ureter	6 h	1 h	Exsanguination
6	M	10	Rectum, bladder	12 h	18 h	Septicaemia, hypotensive shock
7	M	18	Rectum, bladder, small bowel	3 days	18 h	Septicaemia, renal failure
8	M	70	Kidney, small bowel, descending colon	36 h	4 h	Septicaemia, cardiac failure
9	M	4	Descending colon, sigmoid colon small bowel	9 h	18 h	Fitting, aspiration pneumonitis

or a retroperitoneal haematoma. These patients were fully explored to exclude any organ injury.

Mortality and morbidity

Among the 48 patients who arrived within 24 h of injury there were six deaths, four resulting from exsanguination from liver or great vessels injury at or shortly after surgery. Among the 22 patients who presented more than 12 h after wounding, there were three deaths, including two septicaemic patients with combined rectal and bladder injury. The details of those who died are described in *Table 3* and underline the potentially fatal consequences of severe injury to the liver, major veins and rectum.

Morbidity was surprisingly little; in particular no infective problem was related to primary closure of the colon. There were only three instances of infection in the abdominal wound. In two of these the debrided entry wound was nearby, and in the third a transverse colostomy had been brought out through the upper end of the midline incision. There was no evidence of deep intra-abdominal sepsis. Perineal drainage for two cases of severe rectal injury did, however, have prolonged infected discharge.

Discussion

The ICRC now has a prominent role in the delivery of surgical care to the war wounded in several conflict areas around the world. In 1990 there were 22 surgical teams in 14 ICRC hospitals – in Kenya, Somalia, Ethiopia, Cambodia, Thailand, Pakistan and Afghanistan. A wide experience is being accumulated; for example, during the past 5 years there have been more than 36 000 admissions of war-wounded patients requiring surgery to the hospitals of Khao-I-Dang, Peshawar and Quetta. Reports have previously been published from these hospitals[3–7].

For geographical and political reasons these ICRC hospitals have been situated some distance from the battlefield. The setting up of the ICRC hospital in Kabul has put the surgical services right at the front line, and many admissions are therefore received within several minutes to a few hours after injury. However, patients from the countryside, seeking the neutrality of the ICRC hospital, will often arrive one to several days later. Such a time difference is likely to influence the surgical management of all wounds, particularly those of the colon.

It was gratifying to achieve in general a successful surgical outcome, and there was no mortality beyond 24 h after surgery. The recorded overall mortality rate was 13 per cent, compared with the overall mortality rate of abdominal injuries from World War II of 24 per cent and from Vietnam of 8·5 per cent[1]. Contributing factors to these satisfactory results were the relative youth of the patients, the durability of the Afghan people, and the low evacuation time in two-thirds of the patients.

Our surgical approach to the repair of intra-abdominal injury followed established procedures[8,9]. The major area of controversy lies probably in the treatment of colonic injury by selective primary repair in half the patients, rather than by colostomy.

The mortality rate from colon wounds in World War II was high, and therefore a policy of mandatory colostomy was promulgated at that time[10]. This has largely remained the policy in military situations[9]. The view also held sway in civilian life for 30 years after the war, despite a few dissenters[11]. It has been challenged, particularly in the last 10 years, with some workers achieving a 52 per cent primary closure rate[12] and recently a 92 per cent primary closure rate[13] for colonic injury.

Therefore, over the past 10 years, there has developed a consensus in the civilian literature towards selective primary repair, and the management of penetrating colonic injury has clearly departed from the military directive of mandatory colostomy. The safety of primary repair is now well established; it can be performed with minimal morbidity and mortality rates[11–16]. In some recent military conflicts as well, gratifying results have been reported after primary repair on selected patients[17–19].

There are very good reasons for advocating mandatory colostomy in a military setting, as the mortality rate related to colon wounds has been considerable, in Vietnam about 15 per cent[20]. The recorded reasons[14,21] for mandatory colostomy are: (1) the inexperience of the surgeon; (2) high velocity effect on the colon; and (3) that the patient may require transfer after initial laparotomy.

In a military setting the conditions are unlikely to be ideal; evacuation and transfer to other hospitals after initial operative treatment are likely. In this situation a colostomy would be vital for safe mangement. However, in the setting of the hospital at Kabul, the patient remained under the care of the operating surgeon.

The effect on the tissue of high velocity injury has been overstated in the past, and has correctly been questioned in wounds of soft tissue, including colon[22,23]. Fragments are the most common wounding agent in war[24], and this was so in Kabul. These fragments have a wide range of impact velocity, often low, and consideration of an imagined high velocity may result in overtreatment. The surgeon does not know the striking velocity of the wounding weapon. He or she can only observe the destructive injury, and must treat the wound as it is seen.

Our experience supports the belief that colostomy is necessary in unfavourable circumstances. This remains unchallenged, especially in any of four situations: (1) shocked patient; (2) other severe intra-abdominal injuries; (3) delay in presentation; and (4) marked faecal contamination. These factors remained our guidelines, particularly for the transverse or left colon.

Nevertheless, in following a policy of selective primary repair, if the injury to the left colon is minor, then primary suture should be considered. If the injury is major, or a resection is required, then a colostomy should be made. The degree of disruption, and consequent faecal contamination, remains an important criterion in the left colon.

However, in the right colon, even with marked contamination from severe disruptive injury, we believe resection and immediate ileocolic anastomosis is indicated. This aggressive policy has support in both military[17] and civilian settings[25].

The treatment of penetrating injury to the rectum is not controversial, and the present cases were managed by standard techniques[26,27]. A diverting colostomy is mandatory, as an end or loop. The rectum should be repaired if at all possible, and presacral drainage through the perineum should be established. A washout to obtain a clean distal rectum is important. Delay, shock and established sepsis in the pelvic soft tissue space contribute to a potentially fatal condition.

The treatment of liver injury follows established principles[28]. It was often noted that nothing needed to be done. Otherwise limited resectional debridement[29] and packing of a viable pedicle of omentum into deep lacerations[30] were used predominantly and successfully. Simple techniques of haemostasis or drainage were sufficient.

In many armed conflicts today weapons with devastating destructive power are used in countries where the medical infrastructure is limited. The ICRC has responded to this by setting up field hospitals to aid the victims of war. War surgery remains a major challenge to surgical judgement and skills.

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References

1. Heaton LD, Hughes CW. Military surgical practices of United States Army in Vietnam. *Curr Probl Surg* 1966, November: 1–59.
2. Robbs JV. The alternative to colostomy for the injured colon. *S Afr Med J* 1978; **53**: 95–7.
3. Coupland RM, Howell PR. An experience of war surgery and wounds presenting after 3 days on the border of Afghanistan. *Injury* 1988; **19**: 259–62.
4. Coupland RM. Technical aspects of war wound incision. *Br J Surg* 1989; **76**: 663–7.
5. Rautio J, Paavolainen P. Afghan war wounded: experience with 200 cases. *J Trauma* 1988; **28**: 523–5.
6. Fasol R, Zilla P, Irvine S, von Oppell U. Thoraco-abdominal injuries in combat casualties on the Cambodian border. *Thorac Cardiovasc Surg* 1988; **1**: 33–6.
7. Morris D, Sugrue W, McKenzie E. On the border of Afghanistan with the International Committee of the Red Cross. *NZ Med J* 1985; **98**: 750–2.
8. Dufour D, Kroman Jensen S, Owen-Smith M, Salmela J, Stening GF, Zetterstrom B. *Surgery for Victims of War*. Geneva: International Committee of the Red Cross, 1988.
9. Bowen TE, Bellamy RF, eds. *Emergency War Surgery*. Nato Handbook, 2nd U.S. revision. Washington D.C.: U.S. Department of Defense, 1988.
10. Ogilvie WH. Abdominal wounds in the Western Desert. *Surg Gynecol Obstet* 1944; **78**: 225–38.
11. Woodhall JP, Ochsner A. The management of perforating injuries of the colon and rectum in civilian practice. *Surgery* 1951; **29**: 305–20.
12. Stone HH, Fabian TC. Management of perforating colon trauma; randomization between primary closure and exteriorization. *Ann Surg* 1979; **190**: 430–6.
13. George SM, Fabian TC, Voeller GR, Kudsk KA, Mangiante EC, Britt LG. Primary repair of colon wounds; prospective trial in nonselected patients. *Ann Surg* 1989; **209**: 728–34.
14. Burch JM, Brock JC, Gevirtzman L *et al.* The injured colon. *Ann Surg* 1986; **203**: 701–11.
15. Matolo NM, Wolfman EF. Primary repair of colonic injuries; a clinical evaluation. *J Trauma* 1977; **17**: 554–6.
16. Shannon FL, Moore EE. Primary repair of the colon: when is it a safe alternative? *Surgery* 1985; **98**: 851–60.
17. Ganchrow MI, Lavenson GS, McNamara JJ. Surgical management of traumatic injuries of the colon and rectum. *Arch Surg* 1970; **100**: 515–20.
18. Nwafo DC. Selective primary suture of the battle-injured colon: an experience of the Nigerian Civil War. *Br J Surg* 1980; **67**: 195–7.
19. Hasmonai M, Torem S, Kam J, Farbstein J, Schramek A. Primary repair of colon injuries. *Isr J Med Sci* 1983; **19**: 116–18.
20. Walt AJ. Management of injuries of the colon and rectum. *Adv Surg* 1983; **16**: 277–97.
21. Ridgeway CA, Frame SB, Rice JC, Timberlake GA, McSwain NE, Kerstein MD. Primary repair vs. colostomy for the treatment of penetrating colon injuries. *Dis Colon Rectum* 1989; **32**: 1046–9.
22. Fackler ML. Ballistic injury. *Ann Emerg Med* 1986; **15**: 1451–5.
23. Fackler ML. Wound ballistics; a review of common misconceptions. *JAMA* 1988; **259**: 2730–6.
24. Kirby NG, Blackburn G, eds. *Field Surgery Pocket Book*. London: HMSO, 1981.
25. Nallathambi MN, Ivatury RR, Shah PM, Rao PM, Rohman M, Stahl WM. Penetrating right colon trauma: the ever diminishing role for colostomy. *Am Surg* 1987; **53**: 209–14.
26. Trunkey D, Hays RJ, Shires GT. Management of rectal trauma. *J Trauma* 1973; **13**: 411–15.
27. Mangiante EC, Graham AD, Fabian TC. Rectal gunshot wounds: management of civilian injuries. *Am Surg* 1986; **52**: 37–40.
28. Feliciano DV, Jordan GL, Bitondo CG, Mattox KL, Murch JM, Cruse PA. Management of 1000 consecutive cases of hepatic trauma (1979–1984). *Ann Surg* 1986; **204**: 438–45.
29. Moore EE. Critical decisions in the management of hepatic trauma. *Am J Surg* 1984; **148**: 712–16.
30. Pachter HL, Spencer FC. Recent concepts in the treatment of hepatic trauma: facts and fantasies. *Ann Surg* 1979; **190**: 423–9.

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Glutamine-enhanced enteral diet improves nitrogen balance without increasing portal ammonia

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Following surgical stress the jejunum actively metabolizes endogenous glutamine, a non-essential amino acid, to produce alanine and ammonia, which augments substrate flow to the liver at a time when oral intake of nutrients is decreased. Oral glutamine supplementation theoretically may modify the response to injury. This study was designed to demonstrate the role of the jejunum in postinjury glutamine metabolism and to evaluate the influence of enteral glutamine supplements on nitrogen and ammonia metabolism after laparotomy and bowel resection in dogs. Oral glutamine in the presence of an intact small bowel significantly improved nitrogen balance (461 mg kg body-weight^{-1} day^{-1}) compared with a control diet (-370 mg kg^{-1} day^{-1}) ($P<0{\cdot}05$, analysis of variance). Removal of the proximal small bowel prevented this beneficial effect of glutamine (-507 mg kg^{-1} day^{-1}). Glutamine-supplemented and control diets were associated with similar portal ammonia concentrations throughout the study.

Recent work has shown that the gastrointestinal tract, following trauma or surgical stress, exhibits increased metabolic activity and enhances substrate flow to support liver metabolism[1–10]. In particular, glutamine, a non-essential amino acid derived from skeletal muscle breakdown, is actively metabolized by the jejunum[2,4,9–11]. Glutamine can be synthesized by most body tissues. It is glycogenic and has two amine moieties: an α-amino group and an amide group. This underlies its importance as a nitrogen transporter and carrier of ammonia from the periphery to visceral organs, so providing precursor nitrogen for the synthesis of purines and pyrimidines in all cells[4,12–14]. Tissues that metabolize glutamine use the carbon skeleton for energy production by metabolism to α-ketoglutarate with subsequent oxidation in the Krebs' cycle. This yields 30 moles of adenosine 5'-triphosphate (ATP) per mole of glutamine, making it as efficient as an energy source as glucose, which generates 36 moles of ATP per mole oxidized. Glutamine has several unique properties which suggest that it plays a role in health and disease. It is the most abundant amino acid in blood with concentrations of 600–650 mmol l^{-1} and is the most abundant in the intracellular free amino acid pool[4,15]. Following injury, operation and sepsis, the glutamine concentration in blood falls by 20–30 per cent and skeletal muscle may be depleted of glutamine by more than 50 per cent. The fall in glutamine exceeds that of any other amino acid and persists during recovery after all other amino acid concentrations have returned to normal[2,3,16,17]. Glutamine and alanine transport two-thirds of the circulating amino acid nitrogen and comprise more than 50 per cent of the amino acids released from skeletal muscle[16–20]. Glutamine is consumed by replicating cells such as fibroblasts, lymphocytes, tumour cells and intestinal epithelial cells[4,20,21]. This may be of significance in patients with large wounds, inflammation associated with infection and/or gastrointestinal dysfunction that prevents enteral feeding. This study was designed to demonstrate the role of the jejunum in postinjury glutamine metabolism and to evaluate the influence of enteral glutamine administration on nitrogen and ammonia metabolism following laparotomy and bowel resection in dogs.

Materials and methods

Following an overnight fast, groups of male and female beagle dogs weighing between 10 and 15 kg were anaesthetized using thiopentone induction and maintained spontaneously breathing with a mixture of halothane, nitrous oxide and oxygen. A laparotomy incision was made from the xiphoid to the fourth nipple line and catheters were placed via branched vessels into the aorta, portal vein, superior vena cava and femoral vein. All catheters were exteriorized to allow repeated blood sampling. Following catheter insertion, the animals underwent a circumferential enterotomy with immediate reanastomosis or 60 per cent proximal enterectomy with reanastomosis. The anastomosis was constructed at the nearest convenient point to the ligament of Trietze. A feeding enterostomy using a small-gauge Foley catheter (12 Fr) was inserted 10 cm distal to the anastomosis. This was also exteriorized.

After operation the feeding enterostomy was connected to an enteral feeding pump to permit continuous enteral infusion of one of two dietary regimens (*Table 1*). The diet consisted of either a standard peptide diet supplying 2 g protein 50 kcal^{-1} kg body-weight^{-1} enhanced with 30 per cent glycine (control) or the standard peptide diet enhanced with 30 per cent glutamine. Both diets were isonitrogenous and isocaloric. The animals were placed in metabolic cages during enteral feeding to allow calculation of nitrogen balance over the 72-h experimental period.

Urine and faeces were collected every 24 h. Complete separation was impossible because a proportion of the faeces was liquid. A homogenate was therefore made and nitrogen content was calculated by a chemiluminescent method which measures total nitrogen on a fixed volume (Antek Ltd., Houston, Texas, USA). Total nitrogen excreted was then calculated in relation to the total volume of urine and faeces excreted (*Table 2*). Blood samples were collected from the portal vein at the following times: fasting; 1, 6, 18, 24, 48 and 72 h after commencement of feeding. The ammonia content of portal blood was measured by a standard enzyme assay technique.

Results

Cumulative nitrogen balance (*Table 2*) showed that on day 1 all groups were in a positive balance with little difference between groups with intact or short intestines. This possibly reflects the fact that total urine and faecal output was less on day 1 than on days 2 or 3 because the animals were sedated

Table 1 *Number of animals in each experimental group*

Operation	Control	30 per cent glutamine
Enterotomy	7	6
Enterectomy	5	6

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Table 2 *Cumulative nitrogen balance*

	Nitrogen (mg kg body-weight^{-1} day^{-1})			
	Control enterotomy	Glutamine enterotomy	Control enterectomy	Glutamine enterectomy
Day 1	53(82)	216(127)	125(125)	236(105)
Day 2	−37(148)	309(176)*	68(234)	−9(469)
Day 3	−370(338)	461(99)*	−160(663)	−507(279)

Values are mean(s.d.). *$P < 0{\cdot}05$ (glutamine enterotomy *versus* control enterotomy, analysis of variance)

Table 3 *Portal ammonia concentrations*

Time from starting feeds (h)	Ammonia (mmol l^{-1})			
	Control enterotomy	Glutamine enterotomy	Control enterectomy	Glutamine enterectomy
0	212(43)	142(44)	203(47)	157(68)
1	252(50)	181(66)	216(61)	225(59)
6	232(105)	205(44)	191(48)	254(77)
18	237(13)	166(96)	190(68)	267(111)
24	294(161)	160(86)	188(54)	227(54)
48	169(120)	124(69)	154(45)	181(137)
72	144(111)	142(35)	155(87)	227(101)

Values are mean(s.d.). Analysis of variance, not significant

regularly in the early postoperative period. By days 2 and 3, nitrogen excretion had increased in all groups except the group with the intact bowel fed the glutamine-supplemented diet. This was statistically significant on days 2 and 3. All other groups lost nitrogen at similar rates on days 2 and 3.

Table 3 shows portal ammonia concentrations. All groups showed no significant change in ammonia released into the portal circulation over the 72-h experimental period.

Discussion

Following surgical trauma, injury or severe metabolic illness, digestion ceases. As a consequence, mobilization of endogenous fuel depots leads to a period of negative nitrogen balance. Without vigorous nutritional support, such a patient will rapidly become protein depleted, which may lead to an increased risk of complications associated with malnutrition, and even death. If recovery ensues and the ileus resolves, digestion of oral nutrients once more becomes the major source of energy and protein for metabolic homoeostasis.

Provision of glutamine via the jejunum during times of severe catabolic stress may have a beneficial effect on the response to trauma. Unfortunately, glutamine in solution is unstable, breaking down to glutamic acid, pyroglutamic acid and ammonia. Glutamic acid is a neurotransmitter and in large doses will cause seizures. Metabolism of glutamine by the jejunum also produces ammonia and theoretically the high levels of ammonia produced by enteral glutamine feeding could be detrimental to catabolic patients, especially those with impaired liver function. There is little clinical experience of enteral feeding with products containing significant quantities of glutamine.

The results presented show that a glutamine-enhanced enteral diet containing 30 per cent glutamine by weight improves overall nitrogen balance following surgical stress in the dog. Portal ammonia levels were not elevated above the control group values by the dose of glutamine used in this study. The improved nitrogen balance did not occur in the animals that had had 60 per cent of the small bowel removed, showing that the jejunum is a major site of glutamine absorption or metabolism following injury. The positive nitrogen balance in dogs with intact jejunum given glutamine would support the use of early enteral feeding immediately after injury, even before the return of normal physiological bowel function.

The mechanism by which this change occurs is unknown. Analysis of amino acid flux across the gastrointestinal tract, and in liver and skeletal muscle, should help to define this mechanism and is the subject of further investigations. The clinical application of these observations also requires further study in patients who require nutritional support to determine whether enteral feeding solutions containing glutamine might have a beneficial clinical effect.

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References

1. Hanson PJ, Parsons DS. Metabolism and transport of glutamine and glucose in vascularly perfused small intestine of the rat. *Biochem J* 1977; **166**: 509–11.
2. Souba WW, Smith RJ, Wilmore DW. Glutamine metabolism by the intestinal tract, invited review. *J Parenter Enteral Nutr* 1985; **9**: 608–17.
3. Souba WW, Wilmore DW. Postoperative alteration of arterio-venous exchange of amino acids across the intestinal tract. *Surgery* 1983; **94**: 342–50.
4. Windmueller HG. Glutamine utilization by the small intestine. *Adv Enzymol* 1982; **53**: 202–37.
5. Windmueller HG, Spaeth AE. Intestinal metabolism of glutamine and glutamate from the lumen as compared with glutamine from blood. *Arch Biochem Biophys* 1975; **171**: 662–7.
6. Wolff JE, Bergman EN, Williams HH. Net metabolism of plasma amino acids by liver and portal drained viscera of fed sheep. *Am J Physiol* 1972; **223**: 438–44.
7. O'Dwyer ST, Smith RJ, Hwang TS. Maintenance of small bowel mucosa with glutamine enriched parenteral nutrition. *J Parenter Enteral Nutr* 1989; **13**: 579–85.
8. Bistrain BR. Recent advances in parenteral and enteral nutrition: a personal perspective. *J Parenter Enteral Nutr* 1990; **14**: 329–34.
9. Klein S. Glutamine: an essential non-essential amino acid for the gut. *Gastroenterology* 1990; **99**: 279–81.
10. Souba WW, Klimberg VS, Plumley DA *et al.* The role of glutamine in maintaining a healthy gut and supporting the metabolic response to injury and infection. *J Surg Res* 1990; **48**: 383–91.
11. Weber FL, Maddrey WC, Walser M. Amino acid metabolism of dog jejunum before and during absorption of keto analogues. *Am J Physiol* 1977; **232**: E263.
12. Marliss EB, Aoki TT, Pozefsky T *et al.* Muscle and splanchnic glutamine and glutamate metabolism in postabsorptive and starved man. *J Clin Invest* 1971; **50**: 814–19.
13. Muhlbacher F, Kapadia CR, Colpoys MF *et al.* Effects of glucocorticoids on glutamine metabolism in skeletal muscle. *Am J Physiol* 1984; **247**: 75–82.
14. Martin DW. Metabolism of purine and pyrimidine nucleotides. In: Martin DW, Mayes PA, Rodwell VW, eds. *Harper's Review of Biochemistry*. Los Altos, California: Lange Book Series, 1980: 113–24.
15. Bergstrom J, Furst P, Noree LO *et al.* Intracellular free amino acid concentration in human muscle tissue. *J Appl Physiol* 1974; **36**: 693–9.
16. Ruderman N. Muscle amino acid metabolism and gluconeogenesis. *Ann Rev Med* 1975; **26**: 245–53.
17. Felig P. Amino acid metabolism in man. *Ann Rev Biochem* 1975; **44**: 933–7.
18. Kapadia CR, Colpoys MF, Jiang Z *et al.* Maintenance of skeletal muscle intracellular glutamine during standard surgical trauma. *J Parenter Enteral Nutr* 1985; **9**: 583–9.
19. Askanazi J, Carpentier YA, Michelsen CB *et al.* Muscle and amino acids following injury: influence of intercurrent infection. *Ann Surg* 1980; **192**: 78–85.
20. Zielke RH, Ozand PT, Tildon JT *et al.* Reciprocal regulation of glucose and glutamine utilization by cultured diploid fibroblasts. *J Cell Physiol* 1978; **95**: 41–9.
21. Ardawi MSM, Newsholme EA. Glutamine metabolism in lymphocytes of the rat. *Biochem J* 1982; **208**: 743–53.

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Short note

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Hypoxaemia and postoperative pulmonary complications

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After abdominal surgery patients are at risk of developing pulmonary complications which may result in oxygen desaturation[1–3]. Current surgical practice is to rely on clinical assessment to detect such postoperative pulmonary complications. Any hypoxaemia suspected clinically is confirmed by arterial blood gas analysis.

In this study the relationship between postoperative pulmonary complications detected by standardized clinical assessment and oxygen desaturation detected by pulse oximetry is examined in patients after laparotomy.

Patients and methods

A prospective study was performed on 100 patients undergoing laparotomy who returned to a general surgical ward without requiring admission to an intensive therapy unit. The following factors were assessed before operation: previous medical history of respiratory or cardiac pathology, current respiratory symptoms or signs, smoking habits, emergency or routine surgery. The patients were examined twice daily for the first 5 days after operation (excluding the day of operation) and were considered to have a postoperative pulmonary complication if two or more of the following respiratory symptoms and signs were detected: cough, shortness of breath, pleuritic chest pain, temperature of more than 38°C, wheeze, crepitations, focal signs of infection or collapse, pleural rub.

Oxygen saturations (S_{aO_2}) were measured twice daily by an independent observer who was unaware of the clinical findings, using a Kontron 7840 pulse oximeter (Kontron Instruments Ltd., Watford, UK). Such machines are in widespread clinical use and, although their accuracy is well described[4–6], the observer was aware of the conditions leading to artifactual readings and suitable precautions were taken[7].

Patients were considered to have hypoxaemia if S_{aO_2} was <90 per cent and to have severe hypoxaemia if S_{aO_2} was <85 per cent[4,8]. Patients with postoperative pulmonary complications were treated with physiotherapy and antibiotics. Oxygen therapy was added if cyanosis or dyspnoea was present.

Results

The mean age of the patients was 61 years with a male:female ratio of 48:52.

Figures 1, *2* and *3* show the incidence of pulmonary complications and hypoxaemia on each day after operation. Hypoxaemia and severe hypoxaemia occurred most frequently on day 1 and then decreased day by day.

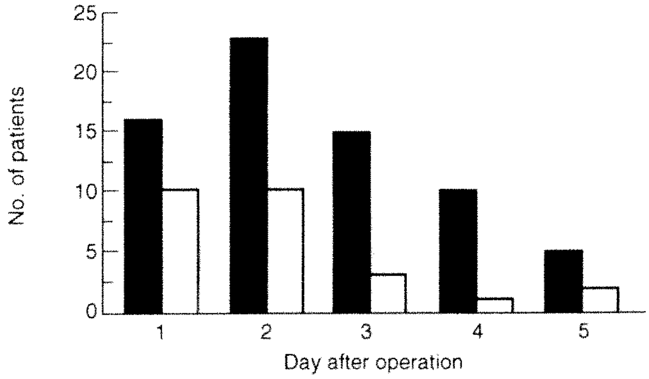

Figure 1 *Incidence of postoperative pulmonary complications for each day after operation, (■) overall and (□) in patients with hypoxaemia* (S_{aO_2} < *90 per cent*)

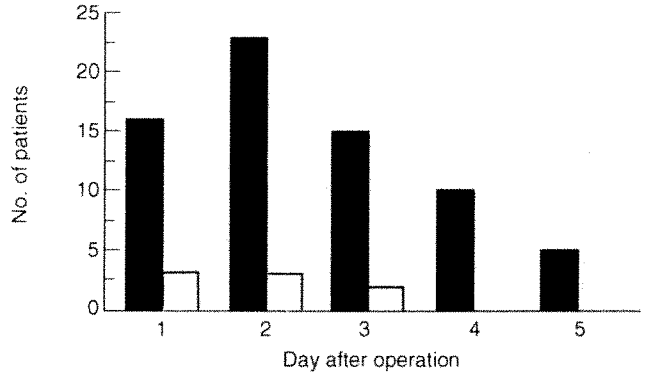

Figure 2 *Incidence of postoperative pulmonary complications for each day after operation, (■) overall and (□) in patients with severe hypoxaemia* (S_{aO_2} < *85 per cent*)

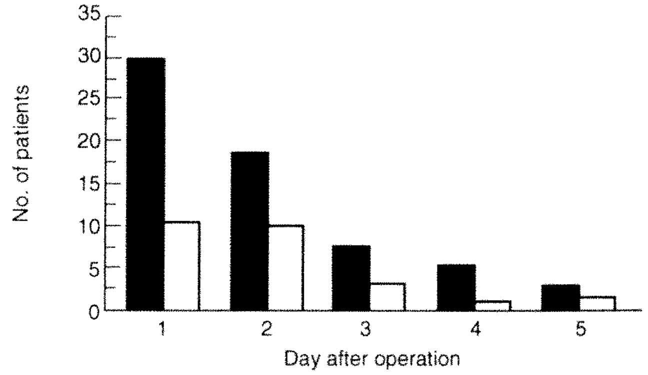

Figure 3 *Incidence of hypoxaemia* (S_{aO_2} < *90 per cent*) *for each day after operation, (■) overall and (□) in patients with postoperative pulmonary complications*

Only a minority of patients with clinically detectable postoperative pulmonary complications were hypoxaemic or severely hypoxaemic. A relatively poor correlation between hypoxaemia or severe hypoxaemia and clinically detectable pulmonary complications was noted for each postoperative day. Of the 30 patients who were hypoxaemic on day 1, 20 did not have postoperative pulmonary complications (*Figure 3*). Of these 20 patients, six went on to develop pulmonary complications on a subsequent postoperative day. Hypoxaemia detected by pulse oximetry on day 1 was thus a predictor of current or subsequent postoperative pulmonary complications in 16 of 30 cases ($P = 0.002$, χ^2 test with Yates' correction). The relationship between severe hypoxaemia and postoperative pulmonary complications was also found to be poor on a day-to-day basis (*Figure 2*). Eight patients were found to be severely hypoxaemic on day 1. Of these eight patients, five did not have postoperative pulmonary complications but two went on to develop them.

Despite the poor correlation between decreased S_{aO_2} and pulmonary complications on each individual postoperative day,

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a stronger correlation emerges between hypoxaemia and pulmonary complications when the 5 postoperative days are considered together. During this period a total of 30 of the patients developed postoperative pulmonary complications determined by clinical assessment using the defined criteria. Thirty-nine patients were found to have hypoxaemia ($S_{aO_2} < 90$ per cent). Twenty of these 39 also developed a pulmonary complication at some time during the first 5 postoperative days, compared with ten of the 61 non-hypoxaemic patients. This increase in the incidence of complications in the hypoxaemic patients was found to be significant ($P = 0.0004$, χ^2 test with Yates' correction). Thirteen patients had severe hypoxaemia ($S_{aO_2} < 85$ per cent) and of these eight also had postoperative pulmonary complications. This was also found to be significant ($P = 0.02$, χ^2 test with Yates' correction). No correlation was found between hypoxaemia or severe hypoxaemia and non-pulmonary postoperative complications.

The preoperative risk factors listed above were subjected to multivariate analysis for postoperative pulmonary complications; only age greater than 85 years was found to have any effect ($P = 0.008$, χ^2 test with Yates' correction). None of the risk factors was found to predispose significantly to hypoxaemia.

Only seven of the 100 patients had oxygen therapy from the first postoperative day onwards, although a larger number received oxygen in the first few hours after operation. Six of these seven had oxygen saturations below 90 per cent, three with severe hypoxaemia. Of the 13 patients with severe hypoxaemia, ten did not receive oxygen.

Discussion

The incidence of hypoxaemia detected by pulse oximetry in this study is high, with 13 per cent of patients developing severe hypoxaemia at some stage during the first 5 days after operation. In a high proportion of patients, both hypoxaemia and severe hypoxaemia go undetected. Only a minority of patients with postoperative pulmonary complications were thought to warrant oxygen therapy.

The incidence of pulmonary complications detected in this study may be greater than commonly seen in clinical practice, owing to the nature and frequency of the documented observations. The incidence of postoperative pulmonary complications detected under similar conditions varies from 14 to 75 per cent[1–3].

Age over 85 years was the only preoperative risk factor which was found to predispose to pulmonary complications in this study, but other authors have found obesity, preoperative respiratory disease, and smoking to be significantly associated[1,3].

The reliability of clinical assessment of hypoxaemia has previously been noted to be poor[9]. The significance of moderate, clinically undetected, hypoxaemia is unknown, but a number of authors have suggested a relationship between hypoxaemia and increased postoperative morbidity[1–3,8,9]. The finding that pulse oximetry demonstrates a high incidence of clinically undetected severe hypoxaemia in patients after operation is important. A prospective controlled trial of the effect of the early detection of this hypoxaemia and its subsequent treatment on postoperative morbidity would seem justified.

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References

1. Hansen G, Drablos PA, Steinert R. Pulmonary complications, ventilation, and blood gases after upper abdominal surgery. *Acta Anaesthesiol Scand* 1977; **21**: 211–15.
2. Egan TM, Herman SJ, Doucette EJ, Normand SL, McLeod RS. A randomized, controlled trial to determine the effectiveness of fascial infiltration of bupivacaine in preventing respiratory complications after elective abdominal surgery. *Surgery* 1988; **104**: 734–40.
3. Vodinh J, Bonnet F, Touboul C, Lefloch JP, Becquemin JP, Harf A. Risk factors of postoperative pulmonary complications after vascular surgery. *Surgery* 1988; **105**: 360–5.
4. Bowes WA, Corke BC, Hulka J. Pulse oximetry: a review of the theory, accuracy, and clinical applications. *Obstet Gynecol* 1989; **74**: 541–6.
5. Yelderman M, New W. Evaluation of pulse oximetry. *Anesthesiology* 1983; **59**: 349–52.
6. Chapman KR, Wiu FLW, Watson RM, Rebunk AS. Range of accuracy of two wavelength oximetry. *Chest* 1986; **1**: 156–60.
7. Severinghaus JW, Naifeh KH. Accuracy of response of six pulse oximeters to profound hypoxia. *Anesthesiology* 1987; **67**: 551–8.
8. Thomson KD, Inoue T, Payne JP. The use of pulse oximetry in post-operative hypoxaemia in patients after propofol induction of anaesthesia. *Int J Clin Monit Comput* 1989; **6**: 7–10.
9. Comroe JH, Botelho S. The unreliability of cyanosis in the recognition of arterial anoxaemia. *Am J Med Sci* 1947; **214**: 1–6.

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Mucosal function after ileal mucosal fenestration and colonic autotransplantation

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A method of small bowel mucosal augmentation called ileal mucosal fenestration and colonic autotransplantation (IMFCA) was devised and tested in pigs. In this technique, a vascularized mucosal graft was harvested from a 12-cm ileal loop, fenestrated by serial incision and then expanded to 20 cm. A 20-cm colonic loop was isolated and surgical mucosectomy was carried out. The fenestrated ileal mucosal graft was then autotransplanted into the prepared colon and the resulting composite structure was exteriorized as a Thiry–Vella loop. With this technique, ileal mucosal fenestrations healed by lateral epithelial in-growth, giving a new mucosal continuum within the recipient colon. At 60 days after surgery, the surface area of transplanted mucosa exceeded that within the original ileal loop by approximately 85 per cent. At this time, the transplanted mucosa had morphology and capacity for Na^+-dependent glucose transport which were indistinguishable from those of control ileal mucosa.

Diminution of the total surface area of small bowel mucosa in short bowel syndrome impairs nutrient absorption. This experimental study describes a new technique aimed at small bowel mucosal augmentation, which involves (1) mucosal expansion from a short donor segment of ileum and (2) colonic autotransplantation. Mucosal expansion is achieved by a fenestration method which induces lateral epithelial ingrowth and formation of neomucosa. The whole technique is called ileal mucosal fenestration and colonic autotransplantation (IMFCA) and has been tested in an animal model.

The success of autograft 'take' and the extent of persistent mucosal expansion and the morphology of IMFCA neomucosa has been assessed. A quantitative assessment of Na^+-dependent glucose transport was carried out in IMFCA neomucosa and compared with transport in control ileal and colonic mucosa.

Materials and methods

Twenty large white (Laplace) pigs were used in this study (female, initial weight 20–24 kg). Ten test pigs underwent ileal mucosal fenestration, expansion and autotransplantation, and ten animals were controls.

Preoperative preparation and anaesthesia

Bowel preparation was standardized in all animals. Liquids only were administered by mouth for 48 h before operation and 500 ml polyethylene glycol solution (30 g l^{-1}) was given 24 h before operation, for mechanical bowel cleansing. A single bolus injection of 750 mg cefuroxime was administered intravenously at induction of anaesthesia. Anaesthesia was induced using a halothane–oxygen mixture by application of a face-mask. Surgical anaesthesia was maintained after endotracheal intubation using a halothane–oxygen mixture administered by a closed non-rebreathing circuit. One litre of normal saline was given intravenously during the surgical procedure via an intravenous cannula to an ear vein.

IMFCA technique

After full aseptic precautions, the abdomen was opened through a midline incision. A 12-cm segment of ileum with its vascular pedicle intact was isolated at a point 20 cm proximal to the ileocaecal valve, and ileal continuity was restored by single-layer silk suture anastomosis. Similarly, a 20-cm loop of apical spiral colon was isolated with an intact vascular pedicle; colonic continuity was restored in a similar manner.

Preparation of the pedicled fenestrated mucosal graft

A stent of silicone tubing (outer diameter 1·5 cm) measuring 20 cm in length was inserted into the lumen of the isolated ileal loop. The serosa and muscle were carefully removed by sharp dissection from this loop, leaving only a thin muscle strip along the mesenteric border, bearing the vascular supply (approximately 10 per cent of loop circumference), and a thin circumferential strip at either extremity. This pedicled mucosal 'tube' was then fenestrated by interdigitating semicircumferential incisions, seven on the antimesenteric border and eight on the mesenteric border, placed approximately 1·5 cm apart. Long incisions were then made in the peritoneum of the small bowel mesentery adjacent to the major arteries. This graft was then expanded to 20 cm in length by gentle traction along the line of the stent, leaving mucosal triangular fenestrations, whose bases each measured approximately 1 cm (*Figure 1*). The mucosal graft was held in this expanded state by seromuscular sutures at each extremity (through the residual circumferential muscle strip) to the ends of the internal 20-cm silicone stent. Despite the tension to sustain expansion, the graft remained pink and healthy.

Construction of the composite ileal–colonic loop

The isolated colonic loop was opened along its antimesenteric border and denuded of mucosa by sharp dissection. The resulting colonic muscle flap with intact vascular pedicle was then closed around the expanded ileal mucosal graft. Colonic muscle was sutured around the islands of ileal muscle at the mesenteric border without compromise to the ileal mucosal vascular supply. Additional silk sutures were inserted through the composite graft at the extremities of the internal silicone stent, which maintained tension and position during healing. The composite graft with silicone stent *in situ* was brought out in the extraperitoneal plane on to the abdominal wall as a Thiry–Vella loop.

Control Thiry–Vella loops

In control pigs, no mucosal dissection was carried out. Thiry–Vella loops of full thickness ileum and colon (12 and 20 cm in length respectively) were brought out on the right and left sides of the abdomen.

Mucosal inspection and biopsy

Following removal of the silicone stent at 2 weeks after surgery, the mucosal surfaces of IMFCA loops were examined using a paediatric sigmoidoscope in all test animals. The examination was repeated at weekly intervals thereafter. Gross mucosal appearances were recorded and the interval taken until complete healing was noted. Biopsies (wet weight 8–10 mg) for light microscopy were taken from the healing edge of fenestrations using flexible endoscopy biopsy forceps, at weekly intervals after stent removal. Biopsies were taken at 14 and 60 days

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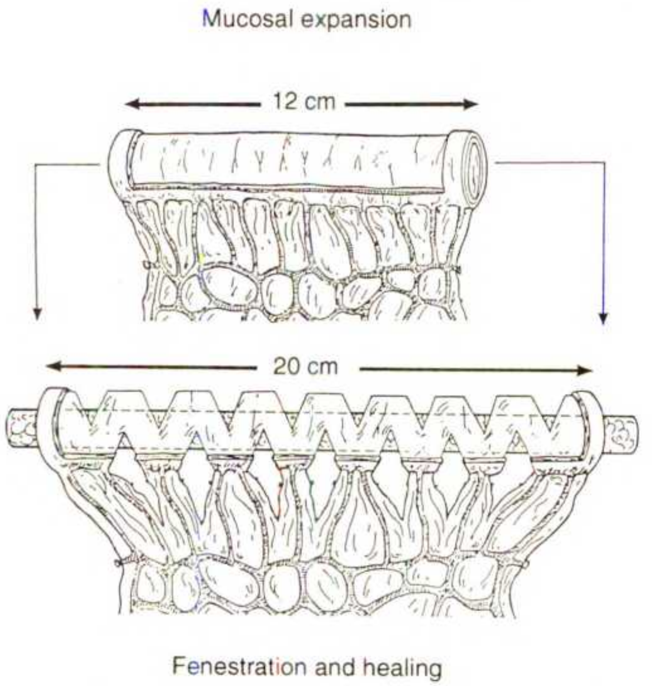

Figure 1 *Preparation of the pedicled mucosal graft. Serosa and muscle were removed from the 12-cm ileal loop, leaving only a thin muscle strip along the mesenteric border and at either extremity. Serial interdigitating incisions were then made through the mucosa on mesenteric and antimesenteric aspects and through the peritoneum of the small bowel mesentery, with preservation of the major vessels. This allowed the loop to be expanded from 12 to 20 cm. Expansion was maintained by suture to an internal 20-cm silicone stent. This expanded ileal mucosal 'tube' was then autotransplanted into the colon*

for brush border membrane vesicle (BBMV) studies. Mucosal biopsies were taken in a similar manner in control loops for BBMV studies at 0, 14 and 60 days.

Preparation of BBMVs from mucosal biopsies

BBMVs were prepared using a cation precipitation and differential centrifugation technique to isolate brush border membranes from basolateral and organelle membranes as previously described by Shirazi-Beechey *et al.*[1].

Assay of Na$^+$-dependent D-glucose uptake

The uptake of D-glucose was measured using a filtration stop technique as described by Shirazi *et al.*[2]. Briefly, 3–8 µl BBMV suspension were placed in medium containing [^{14}C]D-glucose and excess Na$^+$ ions to impose the Na$^+$ gradient required for active glucose transport. At the end of each incubation interval, a stop solution containing phloridzin, which is a competitive inhibitor of Na$^+$ transport, was added to the BBMV suspension. In control experiments, the stop solution was added before the incubation solution. BBMVs were separated from the incubation medium by filtration and the radioactivity retained on the filter was measured in a scintillation counter.

Light microscopy

Tissue was fixed in buffered 4 per cent formaldehyde. Standard haematoxylin and eosin sections were prepared for the histopathological study[3].

Perfusion absorption studies

Perfusion absorption studies were carried out by the technique of Krejs *et al.*[4]. Briefly, a Foley catheter was inserted into each end of the Thiry–Vella loop and the balloons were inflated to occlude the stomas. The loop was then perfused with 200 ml Krebs' solution to which [^{14}C]glycerol trioleate with bile and lipase had been added. This was circulated continuously through the loop within a closed system for 2 h. A perfusion containing [^{3}H]alanine was used on one occasion, in two normal ileal loops (see below).

Perfusion studies in IMFCA loops were deferred until complete healing of fenestrations, i.e. at 6–8 weeks after surgery. Only a slight degree of shrinkage was observed in IMFCA loops at this time but contracture was marked in control ileal Thiry–Vella loops, rendering them unsuitable for perfusion. Therefore, absorption in IMFCA loops which had been defunctioned for 6–8 weeks was compared with absorption in 12-cm loops of normal ileum which were taken 'fresh' from enteric circulation from a point 20 cm proximal to the ileocaecal valve at 14 weeks after surgery. Reproducibility was assessed by repetition of perfusion studies in all four normal ileal loops after an interval of 24 h.

Evaluation of mucosal surface areas in IMFCA and control loops

All animals were killed by sodium thiopentone overdose at 14 weeks after the initial surgery. Control ileal Thiry–Vella loops were very contracted at 14 weeks after initial surgery, so surface area comparisons were made between (1) IMFCA loops; (2) control Thiry–Vella loops; and (3) 12-cm loops of normal ileum which were taken from a point 20 cm proximal to the ileocaecal valve, as described above. All loops were opened along their long axis, and their length and breadth were measured for calculation of surface areas.

Statistical analysis

Descriptive statistics were employed in this study. All data are expressed as mean(s.e.m.).

Results

Two test pigs and three controls died from intestinal obstruction resulting from adhesions. Successful graft 'take' was observed in all surviving test pigs.

Evaluation of healing

Mucosal fenestrations became progressively smaller and irregular, and by 6–8 weeks, healing appeared macroscopically complete in all test animals. Serial biopsies showed that fenestrations were initially covered by a flat featureless epithelium although recovery of villous architecture occurred within 8 weeks of surgery. At the end of the study, mucosal appearances were homogeneous across the whole surface area of IMFCA loops (*Figure 2*).

BBMV studies

Aminopeptidase is a marker enzyme characteristic of the intestinal brush border membrane, while K$^+$-activated phosphatase is characteristic of basolateral membrane. Characterization studies showed a 10–12-fold enrichment in the specific activity of aminopeptidase N in the BBMVs over that of the initial homogenates, and negligible enrichment of K$^+$-activated phosphatase, which confirms that vesicles were derived from intestinal brush border and were free of contamination by basolateral membranes. BBMVs were approximately 1–4 µm in diameter.

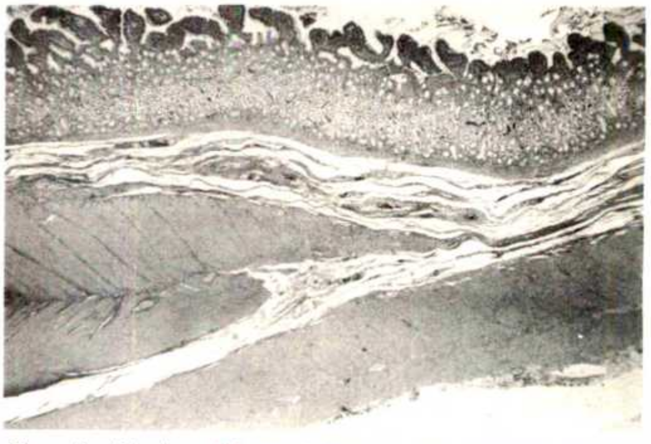

Figure 2 *Histology of the total ileal mucosal fenestration and colonic autotransplantation (IMFCA) loop at 14 weeks after surgery. The section shown was taken from the edge of the IMFCA loop, where the residual rim of ileal muscle has been overlapped by colonic muscle. The mucosa retains villous architecture and is homogeneous throughout. Villi are slightly blunted, probably as a result of prolonged defunction*

Na$^+$-dependent glucose uptake in BBMVs

Na$^+$-dependent D-glucose uptake in BBMVs prepared from control ileal mucosa was highest on the day when the ileal Thiry–Vella loop was created. Uptake declined progressively as the ileal loop remained out of enteric circulation. Initial biopsies of IMFCA neomucosa were taken from the region of healing fenestrations at 14 days after surgery. At this time, Na$^+$-dependent D-glucose transport was low, but improved as healing progressed. At 60 days after surgery, Na$^+$-dependent D-glucose transport rates were similar in control ileal mucosa and IMFCA neomucosa. Uptake in control colonic mucosa was negligible throughout (*Table 1*).

Mucosal surface area

Contracture occurred in all Thiry–Vella loops and was most marked in control ileal loops (*Table 2*). Shrinkage was modest in IMFCA loops, whose mucosal surface area at 14 weeks after surgery exceeded that of 12-cm loops of normal ileum removed at this time (*Figure 3*). IMFCA loops were completely covered by mucosa of homogeneous appearance at the time of removal.

Table 1 *D-Glucose uptake in brush border membrane vesicles (pmol mg protein^{-1} s^{-1})*

Day	IMFCA neomucosa	Control ileum	Control colon
0	–	47·8	0·6
14	12·2	42·8	0·0
60	37·3	31·3	0·0

IMFCA, ileal mucosal fenestration and colonic autotransplantation

Table 2 *Loop dimensions at 14 weeks*

	Thiry–Vella loop			
Dimension	Composite loop	Control colon	Control ileum	Normal ileum*
Length (cm)	17(0·7)	17·6(0·3)	4·8(0·2)	12·0
Surface area (cm^2)	85·3(9·4)	83·3(13·8)	7·6(1·8)	45·9(0·9)

Values are mean(s.e.m.). * The 12-cm normal ileal loop was removed from intestinal continuity in four test pigs at 14 weeks. Note the marked shrinkage of control ileal Thiry–Vella loops

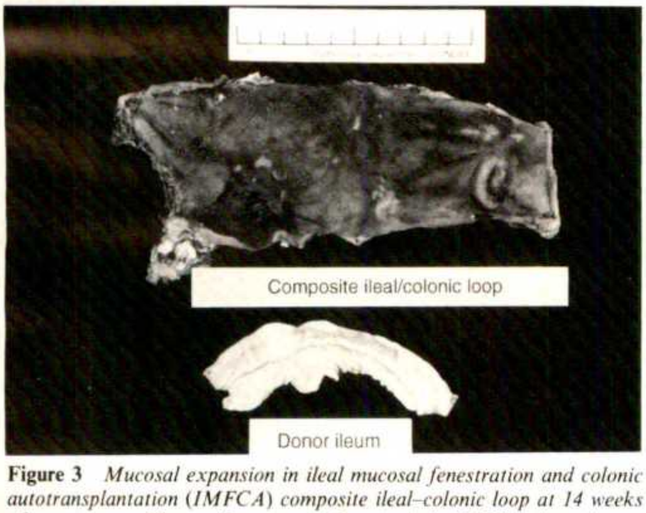

Figure 3 *Mucosal expansion in ileal mucosal fenestration and colonic autotransplantation (IMFCA) composite ileal–colonic loop at 14 weeks after surgery. The surface area of a typical IMFCA loop (upper specimen, labelled composite ileal/colonic loop) is compared with a 12-cm loop of normal ileum (labelled donor ileum because the dimensions of this loop are identical to those of the 'donor' loop from which the mucosal graft was prepared). Both loops have been opened along their long axes to expose the mucosal surface. The IMFCA loop measured 17·8 × 6·1 cm whereas the normal ileal loop measured 12·0 × 4·0 cm*

Perfusion absorption studies

Absorption of 30, 38 and 40 per cent of perfused [^{14}C]glycerol trioleate was demonstrated after 2 h of perfusion in three of the four normal ileal loops shortly after they were removed from enteric circulation. Test reproducibility was poor. On repeat testing, afer an interval of 24 h, absorption of 25 and 20 per cent, respectively, of radiolabelled nutrient was demonstrated in only two loops. Absorption of 19, 25 and 26 per cent of [^{14}C]glycerol trioleate was demonstrated in three of the four IMFCA loops at 8 weeks after surgery.

No demonstrable absorption of [^{3}H]alanine was found in either of two normal ileal loops.

Discussion

This project has designed and evaluated a new technique for small bowel augmentation. IMFCA achieves mucosal expansion by induction of lateral epithelial growth. It exploits a similar principle to that of epidermal expansion by fenestrated split skin grafts[5]. After autotransplantation, fenestrations healed to form a homogeneous mucosal continuum over the entire colonic muscle surface area, over an interval of 6–8 weeks. This IMFCA mucosa retained villous morphology which was indistinguishable from that of control ileal mucosa. In both, villi were slightly blunted, probably as a result of diversion of intestinal content inherent in the study design[6]. Despite shrinkage of IMFCA loops, their mucosal surface area at 14 weeks after surgery exceeded that of 12-cm loops of normal ileum by a factor of 85 per cent. Hence, this study has shown that ileal mucosa may be reliably expanded by the IMFCA technique, and that it flourishes and retains ileal morphology after autotransplantation into colon.

The next objective was a quantitative assessment of mucosal absorptive function in IMFCA and control ileal loops. Experience with perfusion absorption techniques was disappointing. The marked shrinkage of control ileal Thiry–Vella loops made perfusion studies impossible and comparison of function could only be made between IMFCA and 12-cm loops of normal ileum, recently removed from enteric circulation. These control and test loops, therefore, had been deprived of the trophic stimulus of luminal content[6] for different intervals, and reliable quantitative comparison of function was not possible. A further complicating factor was that the perfusion studies in this study had poor quantitative reproducibility in normal 12-cm ileal loops, which suggests that they may be unsuitable for short lengths of bowel.

For these reasons, studies of Na$^+$-dependent glucose uptake in BBMVs were carried out in IMFCA and control mucosa. This method had certain advantages: (1) it gave a quantitative assessment of absorptive function of IMFCA neomucosa against control; (2) the regenerating IMFCA neomucosa could be sampled directly, at intervals, without undue disturbance to the healing process since minute endoscopic biopsies (8–10 mg wet weight) were sufficient for this assay; and (3) Na$^+$-dependent glucose transport is a function only of small bowel and not of colonic epithelium[7]. Hence, this technique provided a measure of differentiation as well as function in the regenerating neomucosa.

In this study, Na$^+$-dependent glucose transport in control ileal mucosa was highest immediately after the loop was removed from the enteric circulation, and declined thereafter. In IMFCA neomucosa, Na$^+$-dependent glucose transport was lower than in control ileum at 14 days after surgery but much greater than in control colon which, as expected, had negligible uptake throughout the study. Hence, at this early stage of the healing process, functional differentiation appeared to precede morphological differentiation. At 60 days after surgery, Na$^+$-dependent glucose transport was similar in control ileal and IMFCA mucosa.

Since perfusion absorption studies were unsuitable in this study, quantitative comparison of absorptive function of entire control and IMFCA loops was not possible. However, mucosal architecture was homogeneous throughout and absorptive function in representative biopsy material was similar in IMFCA and control ileal Thiry–Vella loops on completion of healing at 60 days after surgery. Hence, the greater surface area of functioning mucosa in IMFCA loops would suggest a proportional absorption advantage.

The preliminary results of this new technique are encouraging. Ileal mucosa may be increased and after colonic autotransplantation it retains ileal morphology and the function for Na$^+$-dependent glucose transport. Further work, however, is required to investigate other absorptive functions and to evaluate the influence of mucosal dissection on the motility of IMFCA loops.

Acknowledgements

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References

1. Shirazi-Beechey SP, Davies AG, Tebbutt K *et al.* Preparation and properties of brush border membrane vesicles from human small intestine. *Gastroenterology* 1990; **98**: 676–85.
2. Shirazi SP, Beechey RB, Butterworth PJ. The use of potent inhibitors of alkaline phosphatase to investigate the role of the enzyme in intestinal transport of inorganic phosphate. *Biochem J* 1980; **194**: 803–9.
3. Bancroft JD, Stevens A. Lipids. In: Bancroft JD, Stevens A, eds. *Theory and Practice of Histological Techniques.* 2nd ed. Edinburgh: Churchill Livingstone, 1982: 217–41.
4. Krejs GJ, Seelig LL, Fordran JS. The effect of protonated 2,4,6 triamino pyrimidine on intestinal transport in the dog ileum *in vivo. Gastroenterology* 1977; **72**: 685–92.
5. Fisher JC. Skin – the ultimate solution for the burn wound. *N Engl J Med* 1984; **311**: 466–7.
6. Rijke RPC, Plaiser HM, Ruiter H, Galjaard MD. Influence of experimental bypass on cellular kinetics and maturation of small intestinal epithelium in the rat. *Gastroenterology* 1977; **72**: 896–901.
7. Wright EM, Gunther RD, Kaunitz JD *et al.* Mechanisms of sodium transport across brush border and basolateral membranes. In: Gilles-Baillian M, Gilles R, eds. *Intestinal Transport.* Berlin: Springer Verlag, 1983: 122–32.

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Secondary surgery for liver trauma

Over a 10-year period from 1980, 46 patients with liver injuries were referred after primary admission to other hospitals. Previous surgery had been performed in 40 cases and the predominant reasons for referral were uncontrollable bleeding and postoperative sepsis with biliary leakage. Of 30 such cases, 19 were treated by liver resection; all were of a limited nature and no major hepatectomies were performed. Only two deaths occurred in these patients and this low mortality rate supports our conservative approach to liver trauma. Other reasons for referral were late biliary stenosis, complicated penetrating injury and intrahepatic haematoma. Three cases were referred with postoperative hepatic failure; two responded to resection of infected necrotic tissue and liver transplantation was attempted in the third. Injuries to liver segments 6 and 7 were those most frequently referred for assistance with bleeding, and all patients were safely transferred after intra-abdominal packing. This injury is particularly suitable for resection by segmentectomy rather than a formal hepatectomy, which has been associated with a high mortality rate in trauma cases. Further patients with intractable injuries might be salvaged by liver transplantation.

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Liver trauma remains a difficult surgical problem and specialized ability with hepatobiliary techniques may be required. The complications are dependent on both the extent and position of the liver wound, the immediate problems being intra-abdominal haemorrhage and devascularization of areas of liver parenchyma. Surgery in the initial stages is directed at control of haemorrhage and resection of devascularized liver tissue; anatomical hepatectomies were widely used to achieve these aims[1,2]. However, units from around the world, including our own, have reported a high mortality rate associated with the use of such procedures in trauma cases, contrasting with a lower risk for other indications[3,4]. This is a review of secondary referrals for liver trauma over the last 10 years, during which limited resections appropriate to the injury were used in preference to formal hepatectomy.

Patients and methods

Over a 10-year period from 1980, 46 patients with liver trauma were referred from local and regional hospitals. Patients were transferred after the development of complications to primary surgery, or after the detection of hepatic involvement during surveillance after abdominal trauma. For urgent referrals because of bleeding, we asked for the liver to be packed before transfer in such a manner as to close the injuries and to avoid packs directly within wounds.

All patients with haemoperitoneum and profound shock were operated on immediately. Surgical access was achieved by long midline incision with a lateral extension as necessary. Blood, clots and packs were evacuated and the primary sources of bleeding identified and controlled initially by tamponade. A full laparotomy was performed to detect injuries perhaps missed in the initial haste. To assess the injury, the liver was liberated by division of both the falciform and triangular ligaments and the sites of active bleeding and the extent of devascularized tissue were noted. Since 1984, intraoperative ultrasonography has been used to relate the injury to the vascular hepatic structures. The Pringle manoeuvre was used both to distinguish the type of bleeding (hepatic venous bleeding is not controlled by this technique) and to control the bleeding to allow haemodynamic stabilization.

For simple wounds without devascularized tissue, bleeding sites were individually controlled by suture ligation with carefully placed fine silk sutures under-running the site of bleeding. Parenchymal bridges were divided to facilitate access to bleeding sites within fissures. Since its introduction, tissue fibrin adhesive has been applied to the raw surface of the liver, after control of the main bleeding sites, to reduce capillary bleeding and bile leaks from divided canaliculi.

For larger injuries with devitalized tissue, resection of liver tissue was limited to the minimum necessary; bisegmentectomy or segmentectomy was the most frequent procedure performed. Subsegmental resection, particularly of necrotic tissue (necrosectomy), was also undertaken, using the lines of injury as the boundaries of resection rather than the anatomical planes. Resections were performed by our routine methods[5], before 1984 by the Kelly clamp technique and since 1984 by use of the CUSA ultrasonic dissector[6] (Cooper Lasersonics Incorporated, Stamford, Connecticut, USA). After control of haemorrhage and before application of tissue fibrin glue, an intrabiliary infusion of methylene blue dye was performed routinely, via the gallbladder, to identify bile leaks. Larger leaks were oversewn and smaller leaks were sealed by the tissue fibrin glue. Biliary drainage, either by T tube in the common bile duct or by a transcystic tube, was performed only in cases of extrahepatic biliary injury; routine cholecystectomy was avoided. All abdomens were drained, prophylactic broad-spectrum antibiotics were begun during the operation, and an early return to oral nutrition was encouraged.

Patients admitted in a haemodynamically stable condition were submitted to a more detailed general and hepatic assessment. All underwent biochemical tests of liver function, plain radiology of the chest and abdomen, and abdominal ultrasonography. All patients with major liver injuries had selective visceral angiography and the liver parenchyma was assessed by dynamic computed tomography (CT). Biliary fistulae were examined by sinography or cholangiography via appropriate drains, always preceded by microbiological culture and antibiotic therapy.

In septic cases with devascularized tissue, necrosectomy along the segmental boundaries was performed using a combination of techniques but mainly with the ultrasonic dissector. This was followed by careful identification of biliary leaks by methylene blue infusion with oversewing of larger leaks.

Biliary reconstructions were performed using standard techniques with a Roux-en-Y loop, where possible achieving mucosa-to-mucosa approximation.

Follow-up was carried out for a minimum of 6 months after surgery; patients with biliodigestive reconstructions are followed for life. Results are given as mean(s.e.m.).

Results

The mean(s.e.m.) age of the 46 patients was 26(2) years (range 9–79 years); 41 patients had suffered blunt trauma in road traffic accidents and five had penetrating injuries. The reasons for referral are shown in *Table 1*. Forty patients were referred after previous surgery.

Fifteen patients were referred when haemorrhage proved surgically uncontrollable at the admitting hospital. This was after a major hepatic resection in three patients (two right and

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Table 1 *Reasons for hospital admission*

	No. of patients
Uncontrollable bleeding	15
Postoperative septic biliary leak	15
Late postoperative biliary stenosis	5
Penetrating injury	4
Intrahepatic haematoma	4
Postoperative liver failure	3
Total	46

one left hepatectomies). The remainder had had attempts at local control, in seven using large catgut mattress sutures. Eight patients were transferred after the positioning of intra-abdominal packs; two arrived with fair haemodynamic control and the remaining six had good control despite the subsequent discovery of significant bleeding. The nature of the bleeding was predominantly venous, only two of the 15 cases being found to have an arterial cause.

Twelve patients had a deceleration-type injury with involvement of liver segments 6 and 7. Five were treated by a bisegmentectomy of segments 6 and 7 and three underwent a segmentectomy of segment 7; all eight patients recovered without complications. In three patients bleeding was not found to be heavy after removal of the packs and was controlled by local techniques. In one of these cases, a right hepatectomy had been performed at the referring hospital and, after continued bleeding, the hepatic artery had been ligated. After operation, the patient developed hepatorenal failure. Angiography demonstrated complete arterial occlusion and the patient died after 2 weeks of intensive medical treatment; a necrotic liver was found at autopsy. A final patient had also had a right hepatectomy and was referred with continued bleeding. This proved uncontrollable as part of the vena cava had been resected with accidental oversewing of the hepatic veins. It was impossible to reconstruct a venous outflow from the liver and the patient exsanguinated.

The remaining three patients referred with haemorrhage had a crush-type injury affecting the central liver segments. Bleeding was controlled in one by a partial resection of segment 1, in another by a resection of segment 3 and in the third by a left lobectomy with local haemostasis of a tear in segment 1.

The 15 patients referred with biliary leak were admitted at a mean of 14·7(3) days after their first operation. Initial surgery had been for haemostasis. Two patients had limited resection of devitalized tissue and the remainder had local control of haemostasis, the large catgut mattress technique being used in seven cases. Six patients were successfully treated by ultrasonically guided percutaneous drainage; the remaining nine were submitted to laparotomy and one of these was found to have a duodenal leak which was responsible for the bile drainage. In the remaining eight patients, a significant area of liver necrosis was responsible for the biliary leakage. Of three patients with a deceleration-type injury, two had a bisegmentectomy of segments 6 and 7 and one a segmentectomy of segment 7. In the five patients with a more central crush-type injury a bisegmentectomy of segments 5 and 8 was performed in three, a segmentectomy of segment 8 in one, and a segmentectomy of segment 5 in another. There were no deaths in this group of patients, although one suffered a pulmonary embolus requiring subsequent anti-coagulation. Two subphrenic collections required reoperation and three fistulae took over 30 days to close.

Delayed biliary stenosis occurred in five patients at a mean time from injury of 12 (range 6–24) months. All the stenoses were below the biliary convergence; two occurred after right hepatectomy, one after the repair of a ruptured hepatic artery, and in two no specific cause was found apart from prolonged pedicle clamping. A biliodigestive anastomosis was performed with a Roux-en-Y reconstruction to the convergence or the dilated left main bile duct in cases after right hepatectomy. All patients remain well at a mean follow-up of 38 months.

Four patients were referred with penetrating wounds, two as a result of firearm injury and two after stabbing. A further stab wound case was referred with postoperative liver failure. All these injuries were treated by necrosectomy and removal of foreign material as necessary. All patients survived without complications.

Four patients were referred with enlarging intrahepatic haematoma, one after operation and the others with lesions developing during hospitalization. One haematoma was subcapsular and was treated by needle aspiration under ultrasonic control. The other three haematomas were central and resolved spontaneously.

Three patients were referred with postoperative hepatic failure after liver resection. In two cases, the hepatic decompensation was worsened by sepsis in residual necrotic liver tissue. In both of these, a hepatic artery ligation had been performed to control bleeding from resection planes (a right hepatectomy and a limited necrosectomy for a knife wound). A significant necrosectomy was performed in both cases, with subsequent amelioration of hepatic function; both patients remain well. In the third case, hepatic dysfunction occurred after a right hepatectomy performed using hepatic pedicle clamping for a crush-type injury. The hepatic artery was found to be completely thrombosed and, in view of the patient's young age, orthotopic liver transplantation was attempted. Unfortunately, sepsis originating from the resected necrotic liver remnant proved to be uncontrollable and he died 4 days after operation.

There were only three deaths in the 46 patients referred secondarily to this hospital with liver injury. In two the liver had infarcted owing to absence of an arterial blood supply, and in the other treatment was not possible after inappropriate initial surgery. Twenty-five limited resections were performed without mortality and with minimal morbidity. The mean hospital stay for the series was 30(3) days (range 5–99 days), greater than would be expected for elective hepatic resection.

Discussion

Formal hepatectomy in trauma patients has been associated with prohibitive mortality rates of 40–60 per cent even in experienced centres[4,7,8]. In this unit, before the introduction of the present policy, there was a 40 per cent mortality rate for major hepatic resection after trauma, although during the same period the mortality rate for elective hepatic resection for non-cirrhotic patients was 1·9 per cent[3]. This study does not compare simultaneously present conservative treatment with the previous more aggressive policy, but the low mortality and morbidity rates from this series of 46 consecutive cases reinforces the conservative approach. It is our view that successful treatment of these frequently complex cases relies on detailed preoperative assessment where feasible, careful operative assessment of the injury with an understanding of its relationship to the segmental anatomy, and proficiency with the specialized techniques of segmental resection and biliary reconstructive surgery.

The majority of patients had undergone diagnosis and surgery before referral and, although the prospect of transferring a patient who is actively bleeding seems daunting, this series confirms that, with careful placement of intra-abdominal packs, these patients can be transferred safely[9,10]. Patients actively bleeding had the minimum of preoperative investigation, but stable patients with severe injuries were studied to assess both the extent of parenchymal devitalization and the relationship of previous surgery to the vascular anatomy. Dynamic CT scan and selective visceral angiography often yielded complementary information and are essential to limit surgery to the minimum necessary.

During the operative assessment, the liver injury needs to

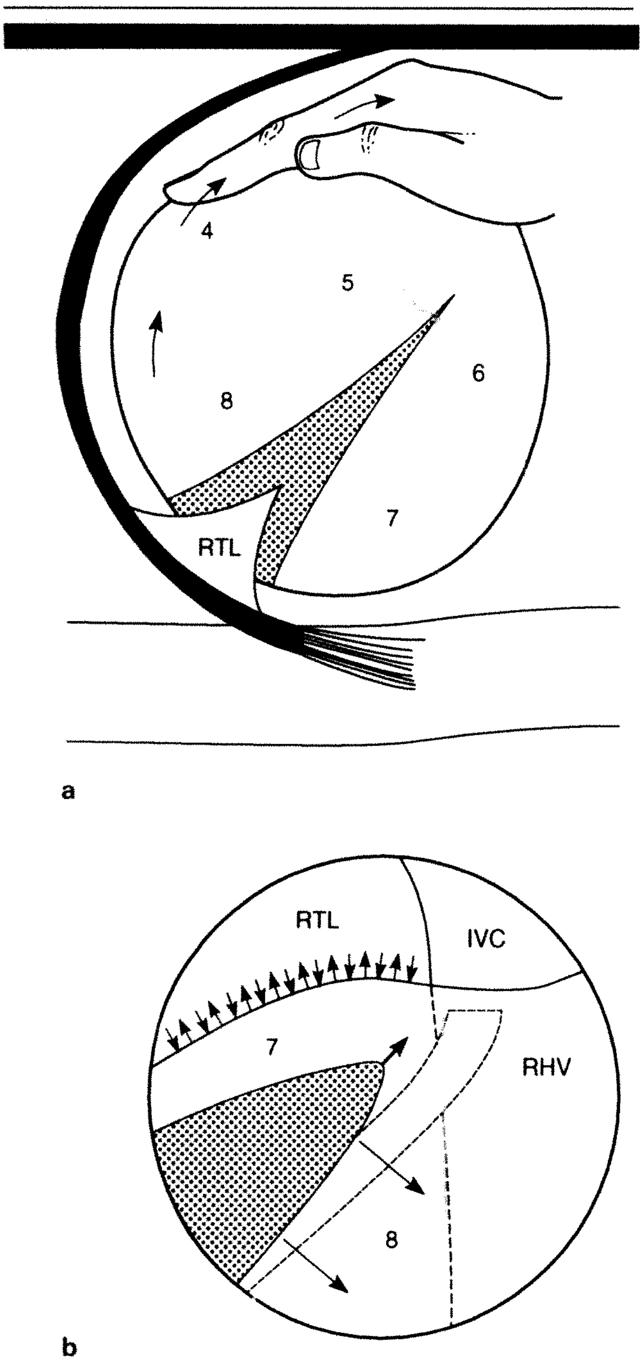

Figure 1 *Schematic diagrams of the mechanism of the deceleration type of liver injury.* **a** *Lateral view of the liver from the right side, showing the relation of the lateral liver segments to the right triangular ligament (RTL). During impact, the ligament restrains the liver, which tears (shaded area) along the line between segments 5 and 8 and segments 6 and 7. Attempts to visualize this region by a hand on the anterior surface of the liver serve only to deepen the wound.* **b** *Close-up view of the medial edge of the wound (shaded area). Attempts to pull on segment 8 serve only to extend the wound towards the right hepatic vein (RHV) or the inferior vena cava (IVC), both of which may then tear. (Numbers represent liver segments)*

be related to the segmental anatomy of the liver[11]. Penetrating injuries may affect any part of the liver, but two main forms of blunt trauma can be identified which affect specific areas of the liver. The deceleration injury, which frequently occurs during motor vehicle accidents, occurs as the liver is violently displaced forwards and results in a fracture along the insertion of the right triangular ligament, the natural restraint of the liver to the diaphragm. This corresponds to the plane of the right portal fissure, separating segments 6 and 7 from the remainder of the liver (*Figure 1a*). This region of the liver is difficult to visualize and full liberation of the liver is needed before the injury can be treated; attempts to view this lesion anteriorly succeed only in worsening the injury and risk extending the wound medially towards the major veins (*Figure 1b*). Of the patients referred with bleeding, 12 had this form of injury and, unless the surgeon is confident with the technique of liver liberation, these injuries are better managed by packing in such a way as to close the tear and transferring the patient to an appropriate specialist unit. The frontal crush injury follows a direct blow to the anterior surface of the liver and results in damage to the central segments 4, 5 and 8. Also affected is the Spigelian lobe, which can be crushed against the spinal column resulting in a source of bleeding which is difficult to control. Such an injury was seen in two patients and necessitated a partial resection in one and local control in the other.

Selective ligation by under-running the bleeding point with fine silk is the ideal method for control of bleeding on the plane of resection or within a fracture[4,12]. We advise against large sutures, with catgut or any other material, which were frequently found in this series to be associated with large areas of necrosis. This has also been shown in other series[13–15] and presumably occurs because the sutures occlude vascular structures lying deep within the parenchyma. In several cases the Pringle manoeuvre[16] was used temporarily to permit haemodynamic stabilization before full assessment, but it was also a valuable aid in identifying and controlling bleeding sites while sutures were inserted. It fails in two instances; major vena caval bleeding is unaffected, and in the presence of an aberrant left hepatic artery the compression is bypassed[17].

Throughout this series, hepatic tissue was removed only as necessary by either subsegmental removal of necrotic material following the lines of injury (necrosectomy) or the limited resection of segmentectomy following anatomical planes[5]. Conservative techniques were introduced in an attempt to reduce the high mortality rate associated with major hepatectomy in liver trauma[18,19] but, while limited resections are becoming more widely employed, formal hepatectomy is still being used[8,17,19,20]. Although comparison between liver trauma series is difficult, it is possible that lack of experience with the limited, but perhaps technically more demanding, procedure of segmentectomy is a factor in the continued use of major hepatectomy. Intraoperative ultrasonography facilitates limited resection, as throughout the procedure the injury can be related to the major vascular structures and the direction of the resection plane can be guided thereby[21].

Injury of the deceleration type presented predominantly as uncontrollable bleeding and was found suitable for treatment by either segmentectomy or bisegmentectomy. A variety of techniques of vascular control can be used during such resection, but we prefer to use the technique of intermittent selective hepatic artery clamping with occlusion of the relevant main branch of the portal vein[22]. The clamps are applied for 15 min followed by 5-min revascularization periods during which the resection plane is reapproximated. Perfusion of the other side of the liver is maintained throughout, splanchnic stasis is avoided, haemodynamic disturbance is reduced to a minimum, and the procedure can be continued safely for over 1 h. The unselected arterial and portal occlusion obtained by the Pringle manoeuvre is another option; it is easy to perform as it does not require preliminary dissection. However, because of concern over the increase in postoperative hepatic cytolysis that has been found after using this method for a lengthy period of time[23], we do not use this technique for vascular control for longer than 15 min. Liver trauma victims frequently have several associated risk factors, including hypovolaemia, coagulopathy, acidosis and hypoxia, which adversely affect the tolerance of the liver parenchyma to vascular clamping. The use of unselective and continuous long-term vascular control during major hepatic resections for liver trauma may have contributed to the reported high mortality rates; several patients in the present series were found to have suffered complications directly attributable to a lengthy Pringle manoeuvre, which might have been avoided by selective intermittent vascular control.

Total vascular exclusion was introduced for use in difficult hepatectomies[24,25] but, whereas in elective cases[26] it can be applied safely for 1 h, hypovolaemic trauma patients often cannot tolerate it because of its severe haemodynamic effects. However, in those with vena caval injury, temporary total vascular exclusion after minimal preliminary dissection was necessary in several cases to identify the site of bleeding from torn hepatic veins before local control. As the majority of our cases are secondary referrals, we have not seen the more extensive injuries to the vena cava reported from other centres[27]. However, rather than use methods such as aortic clamping with the insertion of atriocaval shunts[28], we prefer to prolong the period of total vascular exclusion, countering the haemodynamic effects by the use of venovenous bypass as is customary during liver transplantation[29].

Selective hepatic artery ligation has previously been a popular method of haemostasis[30] but, although it stops arterial bleeding, we are not alone in reporting its risks. Two patients suffered fatal complications and two others suffered temporary hepatic decompensation[31,32]. The inconsistent arrangement of the intralobular hepatic arterial collateral might explain why ligation fails disastrously in some cases[33]. In our view, hepatic artery ligation should always be selective, and should be used only for cases with deep fissuring and arterial bleeding. In three cases where haemostasis appeared doubtful, a fine silicone tube was looped around the hepatic artery so that, if haemorrhage recurred, traction would provide temporary hepatic artery occlusion. Although the slings did not prove necessary in this series, the effectiveness of the technique has been demonstrated in cases of haemobilia[34].

Although six of the patients presenting with septic bile leaks were successfully managed by establishing adequate drainage, in eight cases the bile leak was associated with extensive necrotic tissue. This was removed by necrosectomy, which has been greatly facilitated by the introduction of the ultrasonic dissector. After appropriate adjustment, necrotic tissue is disintegrated and aspirated preferentially, leaving the viable parenchyma *in situ*[6]. In the absence of generalized sepsis, it may even be advantageous to wait several days to allow clear demarcation to develop between the necrotic and vascularized areas of the liver. It is interesting that the cases referred with significant devitalized tissue and bile leakage resulted from a frontal crush-type injury and consequently the more central segments (5 and 8) were the most commonly resected. If found, the bile leak was oversewn, but residual biliary leaks invariably settled once necrotic tissue was removed and adequate drainage of cavities had been achieved. Omental packing was not used as has been advocated elsewhere[35], nor was routine drainage of the biliary tract undertaken in the absence of a biliary anastomosis[36]. The problem of biliary leaks from the plane of the liver resection has been considerably reduced by the routine use of tissue fibrin adhesive.

The penetrating wound was treated similarly by necrosectomy using ultrasonic dissection, and delayed biliary stenosis was reconstructed by standard techniques with long-term follow-up[37]. The progress of both subcapsular and intrahepatic haematoma can be successfully monitored by ultrasonography, with conservative management if asymptomatic, aspiration being reserved for the larger symptomatic lesion[38,39].

The three cases of liver failure all had vascular insufficiency of the liver remnant and, although transient decompensation is relatively common after a large resection, two patients in this series were precipitated into hepatic encephalopathy by sepsis. Recovery followed removal of the infected necrotic tissue with compensatory hypertrophy of the surviving liver. In the other cases, the liver remnant was entirely necrotic and uncontrolled sepsis led to the failure of transplantation.

In this series of secondary referrals for liver trauma, 25 limited resections and one liver transplant were performed. Three patients died from untreatable complications although two of these deaths might have been prevented by avoiding hepatic artery ligation at the first operation. Liver transplantation will have a greater role in the future, not to treat the initial injury, but to salvage cases of severe liver failure after inappropriately aggressive resection or vascular accident to the liver remnant. To be suitable, candidates would need to be free from sepsis and other major organ injuries, with liver vascularization shown to be inadequate for recovery.

Liver trauma will often occur at a distance from the limited number of specialized hepatobiliary services; receiving centres need to be able to provide initial treatment. The principle is to stop bleeding without causing further damage to the liver parenchyma; successful management relies on accurate anatomical assessment. The conservative approach using the more limited resections of segmentectomy and necrosectomy appears to carry a reduced risk compared with the more aggressive approach previously in use, involving the classical hepatectomies. Intra-abdominal packing permits surgeons in district general hospitals to transfer patients safely to a specialized centre.

References

1. Poulos E. Hepatic resection for massive liver injuries. *Ann Surg* 1963; **157**: 525–30.
2. Payne WD, Terz JJ, Lawrence W. Major hepatic resection for trauma. *Ann Surg* 1969; **170**: 929–34.
3. Bismuth H, Castaing D, Houssin D. Die Leberresektion. Indikabionen und Ergiebnisse. *Chirurgie* 1985; **56**: 203–10.
4. Moore FA, Moore EE, Seagraves A. Non-resectional management of major hepatic trauma. *Am J Surg* 1985; **150**: 725–32.
5. Bismuth H, Houssin D, Castaing D. Major and minor segmentectomies 'reglees' in liver surgery. *World J Surg* 1982; **6**: 10–24.
6. Hodgson W, Delguerio L. Preliminary experience of liver surgery using the ultrasonic scalpel. *Surgery* 1984; **95**: 230–4.
7. Walt AJ. The mythology of hepatic trauma or Babel revisited. *Am J Surg* 1978; **136**: 12–18.
8. Carmona R, Lim R, Clark G. Morbidity and mortality in hepatic trauma: a 5 year study. *Am J Surg* 1982; **144**: 88–93.
9. Calne RY, McMaster P, Pentlow BD. The treatment of major liver trauma by primary packing with transfer of the patient for definitive treatment. *Br J Surg* 1979; **66**: 338–9.
10. Hollands MJ, Little JM. Perihepatic packing: its role in the management of liver trauma. *Aust NZ J Surg* 1988; **59**: 21–6.
11. Couinaud C. *Le Foie: Etudes Anatomiques et Chirurgicales*. Paris: Masson, 1957.
12. Pachter HC, Spencer FC, Hoffstetter SR, Coppa GF. Experience with the finger fracture technique to achieve haemostasis in 75 patients with severe liver injuries. *Ann Surg* 1983; **197**: 771–9.
13. Olsen WR. Late complications of central liver injuries. *Surgery* 1982; **92**: 733–40.
14. Lim R, Lau G, Steele M. Prevention of complications after liver trauma. *Am J Surg* 1976; **132**: 156–61.
15. Feliciano DV, Jordan G, Bitondo C, Mattox K, Burch J, Cruse P. Management of 1000 consecutive cases of hepatic trauma. *Ann Surg* 1986; **206**: 438–43.
16. Pringle JH. Notes on the arrest of hepatic haemorrhage due to trauma. *Ann Surg* 1908; **48**: 541–9.
17. Moore E. Critical decisions in the management of hepatic trauma. *Am J Surg* 1984; **148**: 712–16.
18. May ET. Lobectomy, sublobar resections and resectional debridement for severe liver injuries. *J Trauma* 1977; **12**: 309–15.
19. Holland MJ, Little JM. The role of hepatic resection in the management of blunt liver trauma. *World J Surg* 1990; **14**: 478–82.
20. Flint LM, Mays ET, Aaron S, Fulton RL, Polk HC. Selectivity in the management of hepatic trauma. *Ann Surg* 1977; **185**: 613–17.
21. Bismuth H, Sherlock DJ. Echoanatomy of the liver and the use of intra-operative ultrasound in liver surgery. In: Najarian J, Delaney J, eds. *Progress in Hepatic, Biliary and Pancreatic Surgery*. Chicago: Year Book Publishers, 1990: 46–61.
22. Makuuchi M, Moim T, Gunven P, Yamazchi S, Hasegawa H. Safety of hemi-hepatic vascular occlusion during resection of the liver. *Surg Gynecol Obstet* 1987; **164**: 155–8.

23. Kahn D, Hukman R, Dent DM, Terblanche J. For how long can the liver tolerate ischaemia? *Eur Surg Res* 1986; **18**: 277–82.
24. Delva E, Barberousse JP, Nordlinger B *et al.* Hemodynamic and biochemical monitoring during major liver resection with hepatic vascular exclusion. *Surgery* 1984; **95**: 309–18.
25. Bismuth H, Castaing D, Garden J. Major hepatic resection under total vascular exclusion. *Ann Surg* 1989; **210**: 13–19.
26. Huguet C, Nordlinger B, Bloch P, Conrad J. Tolerance of the human liver to prolonged normothermic ischaemia: a biological study of 20 patients submitted to extensive hepatectomy. *Arch Surg* 1978; **113**: 1778–851.
27. Ciresi KF, Lim RC. Hepatic vein and retrocaval injury. *World J Surg* 1990; **14**: 472–7.
28. Rovito PF. Atrial caval shunt in blunt hepatic vascular injury. *Ann Surg* 1987; **205**: 318–21.
29. Shaw BW, Martin DJ, Marquez JM *et al.* Venous bypass in clinical liver transplantation. *Ann Surg* 1984; **200**: 524–34.
30. Mays ET, Conti S, Fallahzadeh H, Rosenblatt M. Hepatic artery ligation. *Surgery* 1979; **86**: 536–41.
31. Lucas CE, Legerwood AM. Liver necrosis following hepatic artery transection due to trauma. *Arch Surg* 1978; **113**: 1107–10.
32. Lucas CE, Flint LM, Polk HC. Selective hepatic artery ligation: limitations and failures. *J Trauma* 1979; **19**: 322–30.
33. May ET. Critical wounds of liver and juxtahepatic veins. *Am Surg* 1977; **43**: 635–45.
34. Bismuth H. Hemobilia. *N Engl J Med* 1973; **288**: 617–19.
35. Stone HH, Lamb JM. Use of a pedicled omentum as an autogenous pack for control of haemorrhage in major injuries of the liver. *Surg Gynecol Obstet* 1975; **141**: 92–4.
36. Lucas CE, Walt AJ. Analysis of randomised biliary drainage for liver trauma in 189 patients. *J Trauma* 1972; **12**: 925–30.
37. Bismuth H. Post operative strictures of the bile duct. In: Blumgart LH, ed. *The Biliary Tract.* Edinburgh: Churchill Livingstone, 1982: 209–18.
38. Geis WP, Schulz KA, Giacchino JL, Freeark RJ. The fate of unruptured intrahepatic haematomas. *Surgery* 1981; **90**: 689–96.
39. Cheatham JE, Smith IE, Tunell WP, Elkins RC. Non operative management of subcapsular hematomas of the liver. *Am J Surg* 1980; **140**: 852–6.

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Case report

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Sarcoma induced by radiotherapy after breast conservation surgery

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The development of sarcoma is a well known complication of radiation therapy and has been reported to occur following irradiation after total mastectomy for breast cancer. We are not aware of sarcoma complicating radiotherapy used in combination with breast conservation surgery and we report two such cases.

Case reports

Case 1

In 1979 a 57-year-old woman had a partial mastectomy, followed by radiotherapy and a 2 year course of chemotherapy for a medullary carcinoma. She received a total irradiation dose of 40 Gy, provided in ten sessions over 26 days, using opposing lateral 18 cm by 16 cm fields. Then, in the treatment arm of the Oxford Breast Trial, she received 24 monthly cycles of melphalan. Although she developed a brisk radiation reaction to the X-rays, she had few side-effects from the treatment.

In 1988 she presented with an ulcerated swelling in the breast at the medial end of the partial mastectomy scar. The lesion was excised widely and was shown to be a completely excised angiosarcoma. The wound healed primarily and no further adjuvant treatment was given.

She developed local recurrence within 2 months and a radical mastectomy was performed. Complete excision was achieved and there was no axillary spread. She was given three cycles of Adriamycin® (Farmitalia Carlo Erba, St. Albans, UK) and ifosfamide.

Three weeks after completion of the chemotherapy there was further recurrence within the skin flaps, and two cycles of VP 16 and high-dose tamoxifen were given. Despite this treatment, local disease progressed and she died at home 2 months later of uncontrolled chest wall recurrence.

Case 2

In 1984, a 42-year-old woman had a moderately differentiated ductal breast carcinoma excised widely. This was followed uneventfully by radiotherapy; 40 Gy were given in ten fractions, three times weekly over 23 days. Tangential fields were used with an 8 Gy, 10 MeV boost to the scar in two fractions over 3 days.

In 1989 recurrent breast cancer was diagnosed by follow-up mammography. Subsequent examination showed two lumps within the breast in the previous irradiation field. Fine needle aspiration cytology confirmed that one was recurrent carcinoma and indicated that the other more peripheral mass was a sarcoma. Mastectomy was advised but the patient demanded local excision of both lesions.

This duly confirmed a poorly differentiated recurrent ductal carcinoma and a malignant fibrous histiocytoma invading muscle; both lesions were incompletely excised. The patient then agreed to a radical mastectomy; the specimen showed no residual tumour and no axillary spread, but the postoperative course was complicated by breakdown of the wound. She has received three cycles of adjuvant Adriamycin and ifosfamide and has remained well 1 year after treatment.

Discussion

In 1957 Sir Stanford Cade reviewed radiation-induced cancer in humans, describing 34 patients which included a personal series of ten patients[1]. One of these patients had a radiation-induced sarcoma after mastectomy and irradiation for breast cancer. He hoped that 'the series of therapeutic cancer are coming to an end'.

During the 1970s and 1980s there continued to be reports of patients who developed radiation-induced sarcoma after total mastectomy and irradiation for breast cancer[2–6].

During the 1980s, there was a trend towards breast conservation surgery, usually combined with radiotherapy. This has resulted in fewer women treated by mastectomy alone and a concomitant increase in the number of irradiated patients.

Radiation-induced sarcoma has not previously been described in the residual breast tissue of women treated by partial mastectomy and irradiation for breast cancer. However,

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as demonstrated by the above two examples, it must be considered in patients developing abnormalities within the radiation fields after such treatment. Sarcomatous change tends to occur 5–15 years or longer after the initial X-ray treatment[6], a longer period than is generally the case for locally recurrent breast cancer. A further distinguishing feature, as demonstrated by our cases, is that sarcomatous change tends to occur in the periphery of the radiation field, whereas recurrent breast cancer is frequently more central.

There is no agreement as to the treatment of radiation-induced sarcoma of the residual breast tissue because of the lack of experience of this rare condition. Both our patients were eventually treated by salvage mastectomy with excision of the underlying pectoral muscle and nodal clearance because of fear of spread to these tissues.

We elected to provide adjuvant chemotherapy, although we admit that the evidence in favour of this relates to limb rather than more central sarcomas. Despite this treatment, we were unable to control the angiosarcoma described for case 1, although this is not an uncommon feature of this particularly aggressive type of tumour.

References

1. Cade Sir S. Radiation induced cancer in man. *Br J Radiol* 1957; **30**: 393–402.
2. Oberman HA, Oneal RM. Fibrosarcoma of the chest wall following resection and irradiation of carcinoma of the breast. *Am J Clin Pathol* 1970; **53**: 407–12.
3. Senyszyn JJ, Johnston AD, Jacox HW, Chu FCH. Radiation-induced sarcoma after treatment of breast cancer. *Cancer* 1970; **26**: 394–403.
4. Gane NFC, Lindup R, Strickland P, Bennett MH. Radiation-induced fibrosarcoma. *Br J Cancer* 1970; **24**: 705–11.
5. Adam YG, Rief R. Radiation-induced fibrosarcoma following treatment for breast cancer. *Surgery* 1977; **81**: 421–5.
6. O'Neil MB, Cocke W, Mason D, Hurley EJ. Radiation-induced soft-tissue fibrosarcoma: surgical therapy and salvage. *Ann Thorac Surg* 1982; **33**: 624–8.

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Erratum

'Randomized study on the effect of collagen impregnation of knitted Dacron® velour aortoiliac prostheses on blood loss during aortic reconstruction' by J. C. A. De Mol Van Otterloo *et al.*, *Br J Surg* 1991; **78**: 288–92.

In the abstract of the above paper the volumes of intraoperative blood lost were transposed. The third sentence from the end of the abstract should read: 'A significant overall difference in intraoperative blood loss between the collagen-impregnated (1907 ml) and the non-impregnated (2425 ml) group was found ($P = 0{\cdot}003$).'

In *Table* 5 the volume of blood transfused for non-impregnated prostheses in the aneurysm group was given as 1000 ml. This volume should have read 1610 ml.

We apologise for these errors and for any confusion caused to the reader.

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A safe new procedure for high-risk patients with symptomatic gallstones

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Cholecystectomy is associated with an appreciable mortality rate in elderly high-risk patients. Patients aged over 60 years with symptomatic gallstones, at high operative risk, underwent cholecystotomy under local anaesthesia through a 3-cm incision. Stones were removed and clearance was demonstrated endoscopically and by tube cholecystography. Catheter drainage was continued for 7 days until a further cholecystogram confirmed clearance. The procedure was attempted in 26 patients with concomitant cardiovascular, respiratory or malignant disease. Successful removal of all gallbladder stones was possible in 24 patients. Four patients had common bile duct stones demonstrated on cholecystography, all of which were successfully treated by endoscopic sphincterotomy. All patients are symptom-free at a mean follow-up of 36 weeks with no recurrent stones on ultrasonography.

Cholecystectomy in the elderly is associated with a mortality rate of 1 to 10 per cent[1-4]. A number of alternative treatments have been introduced to eliminate stones without removing the gallbladder. Oral dissolution agents (chenodeoxycholic and ursodeoxycholic acid)[5], direct gallstone dissolution with methyl *tert*-butyl ether[6] and extracorporeal shockwave lithotripsy (ESWL)[7] have been used. These alternatives to cholecystectomy are effective in selected groups of patients and clearance of stones can be accompanied by relief of symptoms[8].

An alternative to cholecystectomy is cholecystlithotomy, but it is seldom employed because stone formation can recur. Following cholecystotomy and removal of calculi, 37-83 per cent of patients develop recurrent stones[9,10]. Recurrences after cholecystlithotomy are likely to result from fragments or stones overlooked at the initial operation. Using new endoscopic and radiological techniques it is possible to ensure complete clearance of the gallbladder after cholecystlithotomy. The aim of this study was to develop a technique for cholecystlithotomy, safely performed under local anaesthesia and intravenous sedation, in elderly high-risk patients.

Patients and methods

Patients over 60 years old with concomitant disease who were at risk for general anaesthesia were enrolled into the study. All patients had symptomatic gallstones and were deemed unsuitable for ESWL and oral dissolution therapy. Informed consent was obtained with the understanding that general anaesthesia and cholecystectomy would be performed if this was necessary. Before operation the patients fasted for at least 8 h and were given ampicillin, gentamicin and metronidazole intravenously before the procedure.

The gallbladder was localized by real-time ultrasonography, paying particular attention to its relationship to overlying liver and colon. The surface marking of the fundus of the gallbladder was marked with an indelible pen, as previously described[11]. The site of the proposed incision was infiltrated with 0·5 per cent bupivacaine and adrenaline, and patients were sedated with midazolam and pethidine. Additional anaesthesia during the procedure was achieved using 1 per cent lignocaine locally or intercostal nerve block.

A 3-cm abdominal incision was made over the gallbladder. The gallbladder fundus was infiltrated with 1 per cent lignocaine subserosally and grasped with Babcock forceps. A 3/0 polyglyconate purse-string suture was inserted and bile was aspirated using an Ochsner gallbladder trocar and cannula. The gallbladder opening was widened and obvious stones were removed using Desjardin's forceps. A cylindrical tailor-made sheath (*Figure 1*) was secured in the gallbladder by the purse-string suture. The gallbladder lumen was examined with a 24 Fr rigid nephroscope (Richard Wolf GmbH, Knittlingen, Germany) using constant irrigation with normal saline. Residual stones were removed directly with forceps or, if large or impacted, they were fragmented with an ultrasonic contact lithotriptor (Richard Wolf GmbH). When stone clearance was confirmed endoscopically a 24 Fr Foley catheter was secured in the gallbladder using the purse-string suture. The wound was closed in layers around the Foley catheter with monofilament polyglyconate sutures. Tube cholecystography was performed to confirm stone clearance and to outline the bile ducts using 30 ml 25 per cent Hypaque contrast (Stirling Research Laboratories, Guildford, UK). Patients were allowed to mobilize and eat and drink on the same day. The Foley catheter was left on free drainage for 7 days. Stone debris and mucus threads were discharged from the gallbladder for up to 3 days after operation. The sutures and catheter were removed between the seventh and tenth day, provided stone clearance was confirmed by cholecystography. Patients were reviewed at 3 months with clinical and ultrasonographic examination. Clinical follow-up was obtained on all patients for the purposes of this study.

Results

Thirty patients were assessed clinically and 26 were considered suitable for the procedure by ultrasonographic examination. Four had inaccessible, contracted gallbladders. Their mean age was 71 years (range 60-87 years) and 15 were women. Eight patients presented with acute cholecystitis and 18 with biliary colic. All were considered unsuitable for ESWL; ten had

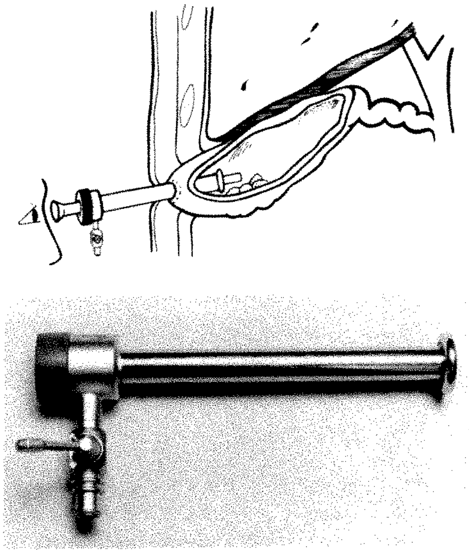

Figure 1 *Sheath for carrying the nephroscope which is introduced from the left through a rubber valve. The tap is for controlling gallbladder irrigation while the flange at the right is held in the gallbladder with a purse-string tie*

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non-functioning gallbladders, five had had unsuccessful ESWL treatment, three had serious concomitant disease and two had acute attacks which failed to settle. Six patients were unsuitable because they were unable to comply with lithotripsy and dissolution therapy or because they chose not to have ESWL. All the patients had serious concomitant disease; 13 had chronic obstructive airways disease, eight had coronary artery disease, four had advanced carcinoma, six had hypertension, five had arthritis, three were on treatment for hypothyroidism, one patient had pulmonary tuberculosis, and one had diabetes. Thirteen were American Society of Anaesthesiologists' grade III and 13 were grade IV[12].

The procedure was successfully performed in 25 patients. One patient had an accidental colotomy and proceeded to repair and cholecystectomy under general anaesthesia. This patient made an uneventful recovery. Of 14 patients who had intercostal nerve blocks, one with emphysema developed a pneumothorax. Eight patients had acute cholecystitis and an empyema was found in three. There was no added difficulty in clearing stones from inflamed gallbladders and, although they were more friable, tearing or perforation did not occur. Four patients had a transient rise in alkaline phosphatase levels. After operation no patient developed hyperamylasaemia or clinical evidence of pancreatitis. In 24 of the 25 patients, tube cholecystography confirmed gallbladder stone clearance. One patient had a residual stone extracted via the cholecystlithotomy tract following fragmentation with a contact lithotripsy probe. Four other patients had common bile duct stones successfully removed by endoscopic sphincterotomy. Two patients had biliary fistulae after catheter removal for 35 and 42 days. Both were managed conservatively.

The mean length of hospital stay after operation was 9 days (range 3–22 days). Recently patients have been discharged on day 3 with tube cholecystography as an outpatient procedure at 7 days. The mean length of follow-up is 36 weeks (range 4–80 weeks). One patient died at 10 weeks from advanced malignant melanoma. All other patients are free of gallbladder symptoms and no recurrent stones have been seen on ultrasonography.

Discussion

The technique described in the present study allows gallstones and gallstone fragments to be removed at a single operation, under local anaesthesia and sedation. The procedure was successful in removing all gallbladder stones in 24 of the 26 patients in whom it was attempted, and this was achieved with a low morbidity rate and no perioperative deaths. Grossly obese patients and those with shrunken gallbladders are probably unsuitable for this procedure, but in practice this led to the exclusion of only four patients.

Gibney *et al.* described the technique of minicholecystotomy and combined this with radiological techniques for stone extraction at a later date[11]. Delaying stone extraction, however, is unnecessary in most patients. Catheter drainage should be maintained for some time after cholecystlithotomy as stone debris and mucus threads are discharged from the gallbladder for up to 72 h. The Foley catheter allows tube cholecystography to be performed on day 7 and in one patient the catheter tract allowed access for removal of an overlooked stone. Assuming that the fundus of the gallbladder becomes adherent to the anterior abdominal wall, this may facilitate percutaneous removal of recurrent stones, should these form in the future.

As an alternative to open cholecystlithotomy, Kellett and colleagues have reported successful removal of gallstones using percutaneous cholecystlithotomy under radiological guidance[13]. This procedure, however, usually requires general anaesthesia.

The high recurrence rate previously reported following surgical cholecystlithotomy may have been due to stones being overlooked at the original procedure. In the present study, endoscopy and cholecystography were employed to ensure that all stones and residual gallstone fragments were removed. Ultrasonic contact lithotripsy facilitates stone removal, and experimental evidence in the urinary bladder suggests that this technique is safe[14]. Electrohydraulic contact lithotripsy has also been safely used in the fragmentation of gallbladder and common bile duct stones[15,16].

In acute cholecystitis, transhepatic or transperitoneal percutaneous catheter drainage of the gallbladder facilitates resolution but gallstone removal or cholecystectomy[17–20] is required later. There are dangers associated with percutaneous puncture of the gallbladder: severe hypotension, bile peritonitis, haemorrhage or inadvertent puncture of the gastrointestinal tract[18–20]. In the present series inadvertent puncture of the transverse colon occurred early in the series but hypotension, haemorrhage and bile peritonitis have not occurred.

Minicholecystotomy with stone removal, under local anaesthesia, appears therefore to offer a therapeutic option in elderly high-risk patients with symptomatic gallstones. It allowed complete stone clearance and resolution of symptoms at a single operation in most patients and, given their age and intercurrent disease, there is little likelihood of stone recurrence becoming a problem in the future.

References

1. Irvin TT, Arnstein PM. Management of symptomatic gallstones in the elderly. *Br J Surg* 1988; **75**: 1163–5.
2. Howton PWJ, Jenkinson LR, Donaldson LA. Cholecystectomy in the elderly: a prospective study. *Br J Surg* 1985; **72**: 220–2.
3. McSherry CK, Glenn F. The incidences and causes of death following surgery for non-malignant biliary tract disease. *Ann Surg* 1980; **191**: 271–5.
4. Addison NV, Finan PJ. Urgent and early cholecystectomy for acute gallbladder disease. *Br J Surg* 1988; **75**: 141–3.
5. Fromm H. Gallstone dissolution therapy: current status and future prospects. *Gastroenterology* 1986; **91**: 1560–7.
6. Thistle JL. Direct contact dissolution of gallstones. *Semin Liver Dis* 1987; **7**: 311–16.
7. Darzi A, Monson JRT, O'Morain C, Tanner WA, Keane FBV. Extension of selection criteria for extracorporeal shockwave lithotripsy. *Br Med J* 1989; **299**: 302–3.
8. Darzi A, Leahy AL, Feeley TM, Tanner WA, Keane FBV. Symptomatology of patients post gallstone clearance in patients receiving ESWL. *Gut* 1989; **30**: A1508.
9. Schildt E. On cholecystolithotomy. *Acta Soc Med Uppsala* 1960; **65**: 91–5.
10. Norrby F, Schonebeck J. Long-term results with cholecystolithotomy. *Acta Chir Scand* 1970; **136**: 711–13.
11. Gibney RG, Fache JS, Becker CD *et al.* Combined surgical and radiological intervention for complicated cholelithiasis in high-risk patients. *Radiology* 1987; **165**: 715–19.
12. Schneider AJL. Assessment of risk factors and surgical outcome. *Surg Clin North Am* 1983; **63**: 1113.
13. Kellett MJ, Wickham JE, Russell RC. Percutaneous cholecystolithotomy. *Br Med J* 1988; **296**: 453–5.
14. Marberger M, Stackl W, Hruby W, Wurster H, Schnedl W. Ultrasonic lithotripsy and soft tissue. *World J Urol* 1985; **3**: 27–32.
15. Chiverton SG, Inglis JA, Hudd C, Kellett MJ, Russell RCG, Wickham JEA. Percutaneous cholecystolithotomy: the first 60 patients. *Br Med J* 1990; **300**: 1310–12.
16. Hwang NH, Lee HH, Lin J, Wang JC, Yueh SK. Transcholecystic endoscopic choledocholithotripsy: successful management of retained common bile duct stones. *Endoscopy* 1987; **1**: 24–7.
17. Werbel GB, Nahrwold DL, Joehl RJ, Vogelzang RL, Rege RV. Percutaneous cholecystostomy in the diagnosis and treatment of acute cholecystitis in high-risk patients. *Arch Surg* 1989; **124**: 782–6.
18. van Sonnenberg E, Wittich GR, Gasola G *et al.* Diagnostic and therapeutic percutaneous gallbladder procedures. *Radiology* 1986; **160**: 23–6.
19. Lohela P, Soiva M, Suramo I, Taavitsainen M, Holopainen O. Ultrasonic guidance for percutaneous puncture and drainage in acute cholecystitis. *Acta Radiol Diag* 1986; **27**: 543–6.
20. Pierce DM, Hawkins IF, Shaver R, Vogel S. Percutaneous cholecystostomy in acute cholecystitis and common duct obstruction. *Radiology* 1984; **152**: 365–7.

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Cystic duct obliteration and gallbladder mucosal destruction: a feasible alternative to cholecystectomy

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'Chemical cholecystectomy' has been proposed as an alternative to removal of the gallbladder. This study assessed cystic duct obliteration using bipolar electrocoagulation (with sham cannulation controls) and gallbladder mucosal treatment with tetracycline (or saline controls) in 29 mongrel dogs. Cystic duct obstruction was assessed by tube cholecystography at day 14, and epithelial damage by histology at day 42. Electrocoagulation by duct diathermy effectively occluded the cystic duct in 14 of 19 animals; however, this was associated with mucocele formation unless mucosal treatment with tetracycline was also performed. Immediate instillation of tetracycline after duct electrocoagulation produced only partial epithelial damage. The combination of duct electrocoagulation and delayed tetracycline instillation at 14 days produced complete destruction of all gallbladder epithelium and an effective chemical cholecystectomy.

During this century, cholecystectomy has remained the mainstay of treatment for symptomatic gallstones. Recent developments in laparoscopic cholecystectomy have given a new impetus to the traditional operation[1]. It is clear, however, that patients coming to surgery now tend to be older, and the surgical mortality rate is higher in this group[2]. The mortality rate for patients over 80 years of age is 7 per cent for elective cholecystectomy and 14 per cent if the operation is performed after acute cholecystitis[3]. Consequently, a number of alternatives to cholecystectomy have been proposed. Cholecystlithotomy, once popular, was largely abandoned in the 1920s because of the high incidence of recurrent calculi. The incidence of recurrent stone formation may be as high as 50 per cent over 3 years and 83 per cent at 15 years[4]. In the 1980s, advances in ultrasonography, dilatation of percutaneous tracts, and endoscopic removal of stones has reawakened interest in cholecystlithotomy[5,6]. Popular acceptance of these procedures is still hampered by the potential for recurrent stone formation.

A number of workers have explored the possibility of ablation of the gallbladder mucosa as a means of preventing recurrent stone formation. Heated 60 per cent diatrizoate meglumine[7], absolute alcohol[7,8] and tetracycline[8] can destroy the mucosa and induce fibrosis. This alone will not prevent re-epithelialization of the gallbladder as ingrowth from the intact cystic duct occurs[9]. Becker and colleagues have recently described a technique whereby long-term occlusion of the cystic duct can be achieved by controlled bipolar radiofrequency electrocoagulation under fluoroscopic guidance[10]. The present experimental study combines the techniques of obliteration of the cystic duct with electrocoagulation, and mucosal destruction with tetracycline, in an attempt to produce a complete destruction of the gallbladder mucosa.

Materials and methods

Twenty-nine male mongrel dogs, weighing 15–24 kg, were used. All were anaesthetized with sodium pentabarbitone (35 mg/kg bodyweight) intravenously, and ventilated with halothane (2 per cent) in room air administered by endotracheal tube. At laparotomy the gallbladder was isolated and a 2–3-cm cholecystotomy was performed. The gallbladder epithelium and cystic duct orifice were visualized (*Figure 1*) using a rigid 24 Fr nephroscope, thus simulating the techniques of minicholecystostomy and endoscopic cholecystlithotomy previously reported[11]. The cystic duct was then cannulated under direct vision using a flexible, polyethylene, electrocoagulation catheter (Wilson-Cook, Winston-Salem, North Carolina, USA), as previously described[12]. Animals were randomized to receive sham cannulation or electrocoagulation. Bipolar electrocoagulation was applied for three periods of 1 s to the origin of the cystic duct, using a radiofrequency generator (Model NL 1804, C. Muller, New Jersey, USA) at a power setting of 50. This produced visible tissue destruction (*Figure 1*). The gallbladder was then closed with chromic sutures over a 12 Fr Foley catheter which was tunnelled subcutaneously and spiggoted to permit subsequent access to the gallbladder. Chemical treatment of the gallbladder mucosa was achieved by instilling 20 ml saline or tetracycline in saline (50 mg/ml), after the contents of the gallbladder had been aspirated.

There were six treatment groups:

Group 1 ($n=5$) Sham cannulation and immediate saline instillation
Group 2 ($n=5$) Duct electrocoagulation and immediate saline instillation
Group 3 ($n=5$) Sham cannulation and immediate tetracycline instillation
Group 4 ($n=5$) Duct electrocoagulation and immediate tetracycline instillation
Group 5 ($n=5$) Duct electrocoagulation and saline instillation 14 days later
Group 6 ($n=4$) Duct electrocoagulation and tetracycline instillation 14 days later

After 30 min exposure, the residual saline or tetracycline was drained from the gallbladder.

Blood was drawn for serum aspartate transferase and amylase estimation on days 0, 1 and 14. Tube cholecystograms were performed under general anaesthesia at day 14 by instillation of 5–20 ml 25 per cent sodium diatrizoate (Hypaque, Sterling, UK), to assess cystic duct patency. At post-mortem examination on day 42, a section of liver, the gallbladder, cystic duct, bile duct, duodenum and pancreas were harvested *en bloc* and fixed in 10 per cent formalin. After preparation, representative slides were stained with haematoxylin and eosin and examined by a pathologist (E.K.) who was not aware of the groups to which the animals belonged. Gallbladder mucosal changes were categorized as normal, demonstrating patchy mucosal destruction with preservation of some epithelium, and complete mucosal destruction with ablation of all epithelium. Also, evidence of histological damage was assessed in the adjacent organs.

Differences in serum aspartate transferase and amylase levels were evaluated by analysis of variance. Fisher's exact test was used to compare results of cystic duct obstruction and mucosal histology.

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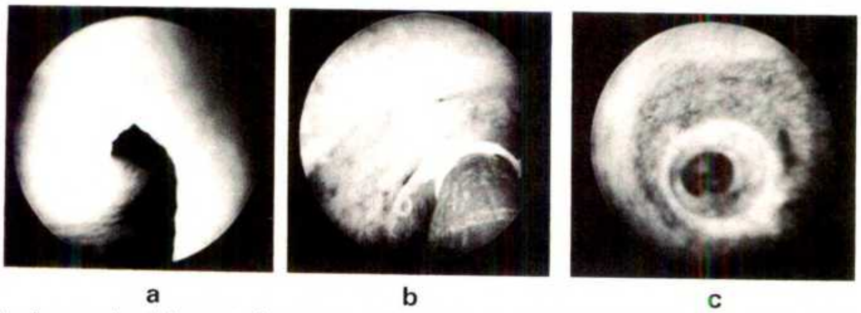

Figure 1 *Three endoscopic photographs of the cystic duct origin.* **a** *Normal cystic duct;* **b** *the electrocoagulation catheter is placed at the cystic duct origin;* **c** *a visible scar is seen after coagulation*

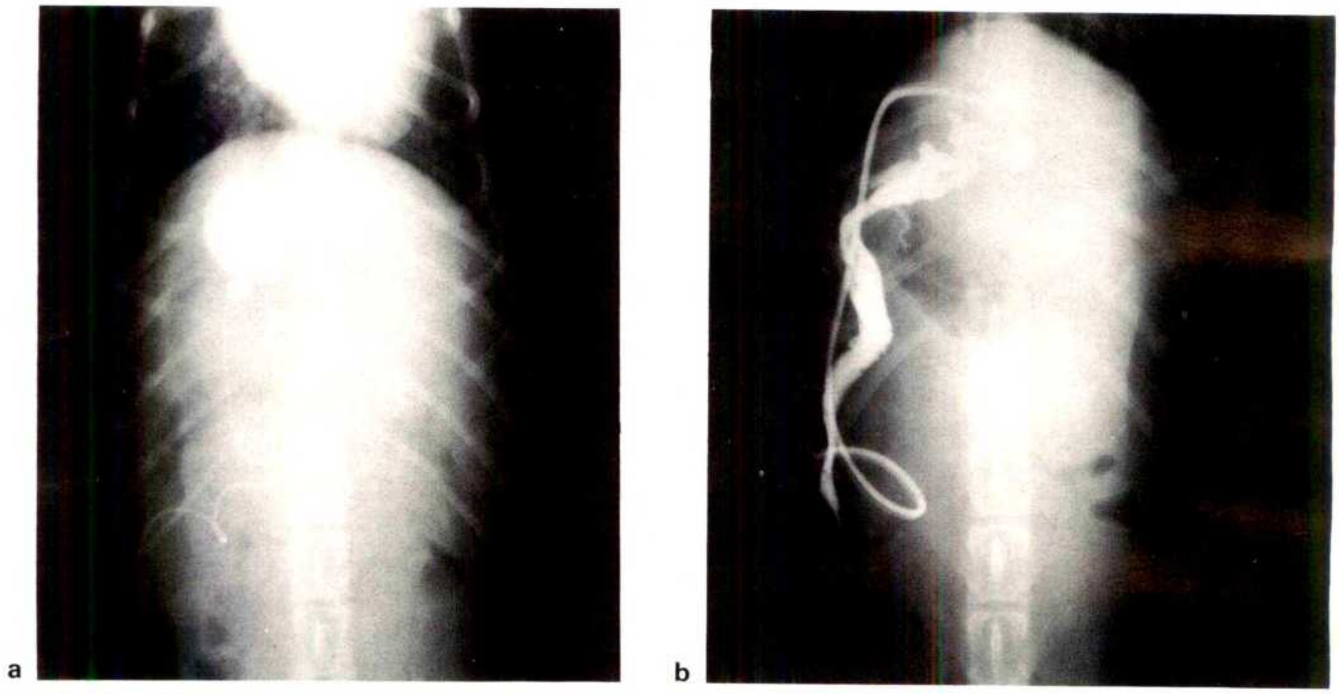

Figure 2 *Tube cholecystography at day 14.* **a** *Radiograph demonstrates a patent cystic duct in a control animal (group 1) with contrast passing into the small bowel.* **b** *The cystic duct of an animal in group 4 (electrocoagulation and immediate tetracycline instillation) is occluded*

Results

None of the animals in group 1 (sham cannulation, saline) or group 3 (sham cannulation, tetracycline) developed cystic duct obstruction at day 14. Following electrocoagulation, 14 of 19 animals had complete obstruction of the cystic duct demonstrated radiologically (*Figure 2*). Two dogs in group 2 (electrocoagulation, saline) and one in each of the remaining groups had a patent cystic duct. The difference between sham-cannulated and electrocoagulated ducts was significant (Fisher's exact test, $P<0{\cdot}01$). Cystic duct obstruction was associated with mucocele formation in three animals in group 2 (electrocoagulation, saline) and in three of four with duct occlusion in group 5 (electrocoagulation, saline at day 14).

None of the animals in groups 1, 2, 3 or 5 developed complete mucosal destruction (*Figure 3*). Two of the five animals in group 4 (electrocoagulation, tetracycline) developed partial epithelial destruction, with preservation of islands of mucosa and mucosal glands (*Figure 4*).

All three animals with cystic duct obstruction in group 6 developed complete destruction of gallbladder mucosa following tetracycline treatment at day 14 (*Figure 5*). When compared with all other groups, the production of mucosal destruction in group 6 was significant (Fisher's exact test, $P<0{\cdot}05$). The combination of duct diathermy and delayed tetracycline instillation produced an effective chemical cholecystectomy.

There was no histological evidence of hepatic, bile duct, duodenal or pancreatic damage in any of the animals. Serum aspartate transferase and amylase levels remained similar to control levels in all groups.

Discussion

The combination of bipolar radiofrequency electrocoagulation and instillation of tetracycline 14 days later produced complete mucosal ablation and an effective chemical cholecystectomy. One animal in group 6 failed to develop an occluded duct and gallbladder sclerosis did not occur in this case. In the present study the effect of repeated electrocoagulation was not studied for animals whose ducts remained patent. Electrocoagulation and saline instillation was associated with mucocele formation. Tetracycline instillation without duct occlusion was not effective, presumably because the sclerosant did not have sufficient time in contact with the epithelium. This also explains why the combination of duct coagulation with immediate tetracycline instillation was only partly effective, as complete duct obstruction is not observed until 10 days after duct diathermy[10].

A number of alternatives to cholecystectomy have been proposed for the treatment of symptomatic gallstones. These include medical treatment with oral bile desaturating agents[13], percutaneous gallbladder cannulation and methyl *tert*-butyl ether instillation[14], extracorporeal shockwave lithotripsy and oral dissolution therapy[15], and percutaneous cholecyst-

Figure 3 *Normal gallbladder mucosal appearance in a group 1 control animals. L, luminal aspect*

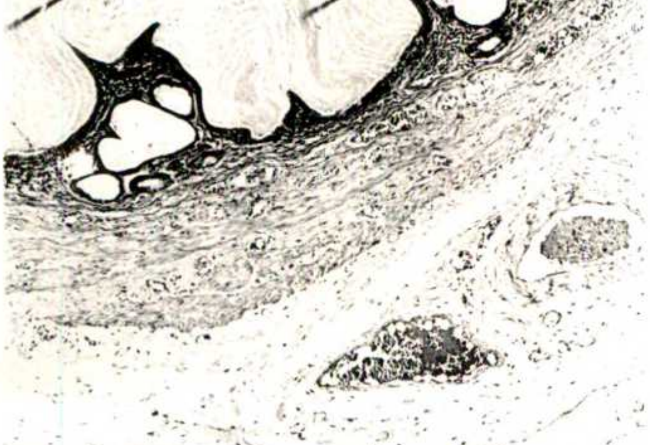

Figure 4 *Duct electrocoagulation and immediate tetracycline instillation (group 4) produces patchy mucosal destruction with regeneration (R) and associated chronic inflammation in gallbladder wall. Intact mucosa indicated by arrow*

lithotomy[5,6]. All of these techniques can effectively eliminate stones from the gallbladder and relieve symptoms, but there is a risk of recurrent stone formation as the diseased gallbladder remains *in situ*. In the present study, a technique of chemical cholecystectomy is proposed which could be combined with these alternative treatments to obviate the need for laparotomy and major surgery. With modification to the technique described, it should be possible to perform this procedure safely, by a percutaneous route under radiological control, similar to the technique described by Becker and colleagues[10].

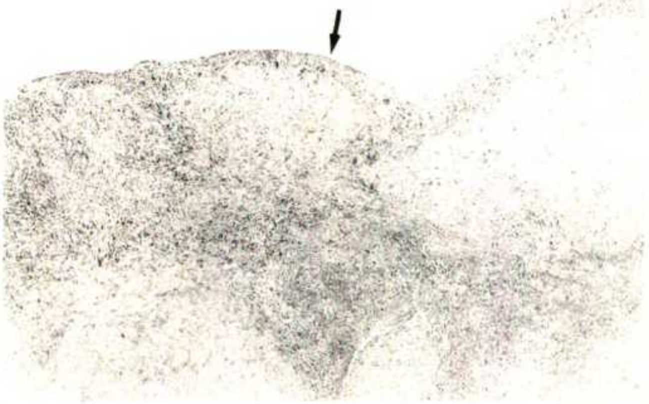

Figure 5 *Complete gallbladder mucosal destruction (arrow) with acute and chronic inflammation in the wall was seen in three of four animals in group 6 (electrocoagulation and tetracycline at day 14)*

The procedure described is not only effective but is also safe. No common bile duct damage occurred in animals with patent cystic ducts in which tetracycline was instilled into the gallbladder. Presumably this is because the sclerosant passed rapidly into the bowel, and the protective/dilutional effect of bile prevented epithelial damage. Getrajdman and colleagues have suggested that sclerosing agents may cause serious hepatic toxicity with centrilobular necrosis in the rabbit[16]. Remley and associates found evidence of mild portal hepatic inflammation in rabbits treated with tetracycline following cystic duct ligation[8]. In the present study there was no elevation in serum aspartate levels and no histological evidence of liver damage in any animal. Similarly, there was no hyperamylasaemia or histological evidence of pancreatitis.

The present study demonstrates that an effective chemical cholecystectomy can be produced. While further studies are undoubtedly required, it seems entirely possible that an effective alternative to cholecystectomy can be proposed. Although a laparotomy was performed for the purpose of the present study, it would be possible to introduce the cholecystoscope, bipolar electrocoagulation catheter and Foley balloon catheter into the gallbladder percutaneously. Percutaneous catheterization of the gallbladder could be followed by stone eradication, cystic duct electrocoagulation and subsequent gallbladder mucosal ablation.

References

1. Reddick EJ, Olsen DO. Laparoscopic laser cholecystectomy. *Surg Endosc* 1989; **3**: 131–3.
2. Editorial. Gallstones, bile acids and the liver. *Lancet* 1989; **ii**: 249–51.
3. Gutman H, Deutsch AA, Nudelman IL, Reiss R. Cholecystectomy for octogenerians. *Dig Surg* 1988; **5**: 189–93.
4. Norrby S, Schoenebeck J. Long-term results with cholecystolithotomy. *Acta Chir Scand* 1970; **136**: 711–13.
5. Kerlan RK, la Berge JM, Ring EJ. Percutaneous cholecystolithotomy: preliminary experience. *Radiology* 1985; **157**: 653–6.
6. Kellett MJ, Wickham JE, Russell RC. Percutaneous cholecystolithotomy. *Br Med J [Clin Res]* 1988; **296**: 453–5.
7. Salomonowitz E, Frick MP, Simmons RL *et al*. Obliteration of the gallbladder without formal cholecystectomy. A feasibility study. *Arch Surg* 1984; **119**: 725–9.
8. Remley KB, Cubberley DA, Watanabe AS, Nelson JA, Colby TV. Systemic absorption of gallbladder sclerosing agents in the rabbit. A preliminary study. *Invest Radiol* 1986; **21**: 396–9.
9. Getrajdman GI, O'Toole K, Laffey KD, Martin EC. Cystic duct occlusion and transcatheter sclerosis of the gallbladder in the rabbit. *Invest Radiol* 1986; **21**: 400–3.
10. Becker CD, Quenville NF, Burhenne RM. Long-term occlusion of the porcine cystic duct by endoluminal radio-frequency electrocoagulation. *Radiology* 1988; **167**: 63–8.
11. Leahy AL, Darzi AW, O'Gorman S, Tanner WA, Keane FBV. Minimal surgery for symptomatic gallstones; a safe, new procedure for high risk patients. *Br J Surg* 1989; **76**: 1343.
12. Becker CD, Jameson M, Fache JS, Burhenne HJ. Catheter for endoluminal bipolar electrocoagulation. *Radiology* 1989; **170**: 561–2.

13. Bachrach WH, Hofman AF. Ursodeoxycholic acid in the treatment of cholesterol cholelithiasis. *Dig Dis Sci* 1982; **27**: 737–56.
14. Allen MJ, Barody TJ, Bugliasi TF, May GR, La Russo NF, Thistle JL. Rapid dissolution of gallstones by methyl tert-butyl ether: preliminary observations. *N Engl J Med* 1985; **312**: 217–20.
15. Darzi A, Leahy AL, O'Morain C, Tanner WA, Keane FBV. Gallstone clearance: a randomized study of extracorporeal shock wave lithotripsy and chemical dissolution. *Br J Surg* 1990; 77: 1265–7.
16. Getrajdman G, O'Toole K, Logerfo P, Laffey KJ, Martin EC. Transcatheter sclerosis of the gallbladder in rabbits. *Invest Radiol* 1985; **20**: 393–8.

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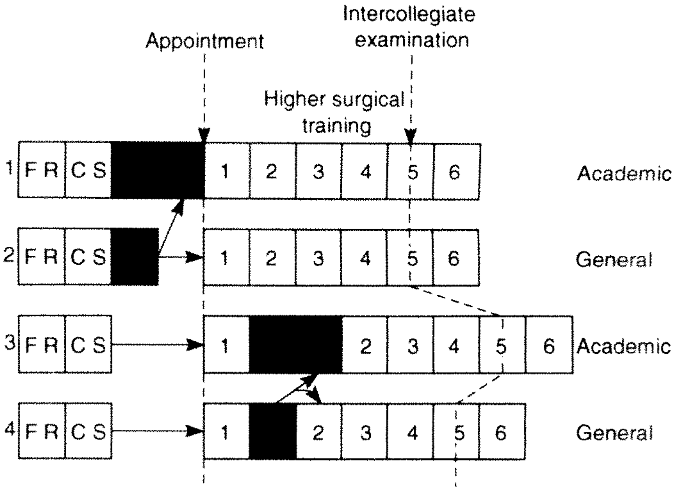
For debate: research in surgical training

There is currently a move towards a more structured training for general surgery in the UK, and the place of research within such a programme has been widely debated, not only in the *Annals of the Royal College of Surgeons*[1–7] but also within the Association of Professors of Surgery, the Association of Surgeons, the Surgical Advisory Committee, the Association of Surgeons in Training and the specialty associations.

At the recent annual general meeting of the Association of Surgeons of Great Britain and Ireland there was general agreement on the following points. It was felt that a period of full-time research has a vital role in the training of a surgeon provided it is well planned and supervised, but the present degree by thesis is not always supervised and does not seem the best model for the majority of surgical trainees in the future. Research opportunities often arise in a haphazard way owing to the uncertainties of 'soft' money funding, but it was generally agreed that the appointment to such a post should be made with the same care as to a clinical post, since it may effectively signal entry into higher surgical training. A preliminary instruction course in research methods and statistics would be greatly beneficial to trainees starting a period of research. This full-time research should be for a minimum of 1 year, but a longer period of 2–3 years should be available to those academic trainees who specifically and realistically wish to do an MD-type thesis. It seems appropriate that slots within research programmes should be inspected with the same vigour as clinical posts. A clear signal is required by those trainees at present in basic surgical training and by appointment committees for career registrars as to what is expected of them, and there is some urgency to reach a consensus rather than to rely on market forces.

However, the best timing for this period of research is not agreed; to facilitate further discussion a series of models has been drawn up (see *Figure*). A few trainees continue to do a PhD-type thesis before sitting the examination for Fellowship of the Royal College of Surgeons (FRCS), but majority opinion is against this as a normal model. On the whole, the academics would like to see the surgeon of the future succeed in research before being allowed into higher surgical training. At this stage they might still go into other specialties (models 1 and 2 of *Figure*). However, the surgeons in training feel that entry to higher surgical training with the award of a career number should depend on surgical ability and not research endeavour. They favour a period of clinical consolidation after passing the FRCS examination and before entering a period of full-time research (models 3 and 4). The Association of Surgeons in Training strongly supports continuous assessment during higher surgical training, and this would seem most important in the first 2 years, whether the trainee is in a research or a clinical slot. There is a call for flexibility to meet the varying needs of trainees and the requirements of academic units; nevertheless, there should be an agreed framework for higher surgical training, and this might mean a choice of two models.

There may be a good case for the award of a 1-year degree, such as a MMedSci, MSc or MPhil, since in most universities these can be extended to a higher degree if the trainee so wishes. On the other hand the intercollegiate examination will also assess the research capability and output of the trainee. Much of the present dissatisfaction stems from a system which relies on 'soft' money funding and this issue must be addressed. If it is accepted that a minimum of 1 year in research is a vital part of postgraduate training for a surgeon, many logically argue that the National Health Service should fund a 1-year period across the board (and across other specialties).



Suggested models for structured research period in higher surgical training. Blocks represent 1-year periods of clinical training (☐) *or research* (■)

Entry into basic surgical training is threatened by the present uncertainties and there is now some urgency to conclude the debate and take executive action.

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1. Taylor I, Johnston IDA. On behalf of the Association of Professors of Surgery. Research and surgical training. *Bull Ann R Coll Surg Engl* 1989; **71**: 89–90.
2. Blandy JP, Browse NS, Hardcastle JD. The place of research in surgical training. *Bull Ann R Coll Surg Engl* 1989; **71**: 64.
3. Bates T. Clinical research in higher surgical training. *Bull Ann R Coll Surg Engl* 1990; **72**: 68–9.
4. Farndon JR. Correspondence. *Bull Ann R Coll Surg Engl* 1991; **73**: 5–6.
5. Rudge CJ. Surgical research for all? *Bull Ann R Coll Surg Engl* 1991; **73**: 25.
6. Celestin LR. Correspondence. *Bull Ann R Coll Surg Engl* 1991; **73**: 55–6.
7. Taylor I. Correspondence. *Bull Ann R Coll Surg Engl* 1991; **73**: 56.

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Tension pneumothorax during laparoscopic cholecystectomy

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Laparoscopic techniques for cholecystectomy are rapidly gaining popularity with surgeons and patients. The procedure is described as safe, with an important reduction in hospital stay and an early return to full activity. We report here an unusual complication of this operation.

Case report

A 50-year-old woman with a history of abdominal pain associated with cholelithiasis was admitted for laparoscopic cholecystectomy. She had undergone no previous abdominal operations but had been uneventfully anaesthetized on several occasions for minor orthopaedic procedures. There was no other relevant medical history. The operation was performed under a total intravenous general anaesthetic, i.e. without inhalation agents. Pneumoperitoneum was achieved using a Verres needle inserted via an infraumbilical site and connected to a variable-flow pressure-controlled insufflator. An initial insufflation was extraperitoneal, but this was rapidly recognized and the gas was allowed to escape. Once correct insufflation of the intraperitoneal cavity had been achieved, the laparoscope was inserted via a 10-mm trocar placed subumbilically. Two 5-mm trocars were inserted in the right subcostal and right anterior axillary line positions, and a second 10-mm trocar was inserted to the right of the falciform ligament in the epigastrium. All trocars were inserted under direct intraperitoneal vision of the laparoscope. Following trocar insertion and before further instrumentation, capillary oxygen saturation fell, ventilation pressures rose and on clinical review a right pneumothorax was diagnosed. This was confirmed by radiology and an intercostal drain was inserted with immediate relief of the pneumothorax. Analysis of the gas obtained from the intercostal drain confirmed a high proportion of carbon dioxide (greater than 10 per cent).

The operation was completed successfully but drainage from the intercostal tube continued throughout the procedure. The chest drain was removed after 24 h, and the patient was discharged from hospital with no further complications. Water-soluble contrast radiology via the intercostal drain showed no obvious connection between the pleural and peritoneal cavities.

Discussion

Laparoscopy is increasingly used by general surgeons as both a diagnostic and therapeutic procedure. It is associated with low but appreciable morbidity and mortality rates. In 1978 the Confidential Enquiry into Gynaecological Surgery[1] reported a mortality rate of eight per 100 000 laparoscopies with complications from cardiac arrhythmias, pulmonary embolism, bowel trauma and haemorrhage.

Since the introduction of laparoscopic cholecystectomy in 1987, several complications associated with the procedure have been reported[2–5]. Most of these are related to the therapeutic procedure and include haemorrhage and bile duct trauma. Perforation of the small intestine by the Verres needle has also been described[2].

Pneumothorax has been reported previously during a laparoscopic procedure[6]. It has been suggested that the underlying cause is a congenital defect of the diaphragm (patent pleuroperitoneal canal) through which the insufflated gas passes into the thoracic cavity. Although in this case no communication could be demonstrated by radiology, a patent pleuroperitoneal canal would account for the sequence of events observed. There was no trauma to the diaphragm during the procedure, the gas removed from the chest was rich in carbon dioxide, and flow of gas via the interpleural drain continued until the pneumoperitoneum was evacuated.

We should like to alert the increasing number of surgeon-laparoscopists to this potentially lethal complication. It was entirely due to careful anaesthetic monitoring that the problem was recognized early and disaster averted.

References

1. Carron Brown JA, Chamberlain GVP, Jordan JA *et al.* The report of the Working Party of the Confidential Enquiry into gynaecological laparoscopy. *Br J Obstet Gynaecol* 1978; **85**: 401–3.
2. Grace PA, Quereshi A, Coleman J *et al.* Reduced postoperative hospitalization after laparoscopic cholecystectomy. *Br J Surg* 1991; **78**: 160–2.
3. Nathanson LK, Shimi S, Cuschieri A. Laparoscopic cholecystectomy: the Dundee technique. *Br J Surg* 1991; **78**: 155–9.
4. Neugebauer E, Troidl H, Spangenberder W, Dietrich A, Lefering R. Conventional *versus* laparoscopic cholecystectomy and the randomized controlled trial. *Br J Surg* 1991; **78**: 150–4.
5. Dubois F, Kard P, Bertheolot G, Levard H. Coelioscopic cholecystectomy. *Ann Surg* 1990; **211**: 60–3.
6. Calverly RK, Jenkins LC. The anaesthetic management of pelvic laparoscopy. *Can Anaesth Soc J* 1973; **20**: 679.

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Subtotal cholecystectomy

Subtotal cholecystectomy has been carried out on 11 patients during a 5-year period, constituting 3·8 per cent of cholecystectomies performed during this time. The indications were severe inflammation/fibrosis in six patients, portal hypertension in three and the Mirizzi syndrome in two patients. There were no deaths and only minor in-hospital morbidity. One patient developed a common bile duct stone 21 months after the operation. None of the remaining patients has to date developed postcholecystectomy sequelae (mean follow-up period 29 (range 1–62) months). Subtotal cholecystectomy is a safe, straightforward and definitive operation in patients for whom standard cholecystectomy could be dangerous, and is a more attractive proposition than cholecystostomy.

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Cholecystectomy is a common surgical procedure. It is, however, a potentially difficult operation because of the variable anatomy and the wide spectrum of inflammatory reaction within the gallbladder and surrounding tissues. On occasion it can test even the most experienced surgeon.

The associated presence of portal hypertension (especially secondary to cirrhosis) further increases the difficulty and danger of the operation. Cholecystectomy in the patient with cirrhosis has been described as a 'formidable operation' with a reported mortality rate of 83 per cent in high-risk cases[1]. It has therefore been suggested that the indications for elective cholecystectomy in patients with cirrhosis should be restricted[2] and that the operation should be performed only when there are life-threatening complications[1].

Subtotal cholecystectomy has been described as an easy, safe and definitive alternative to standard cholecystectomy for the difficult gallbladder and in the presence of portal hypertension[3]. More recently this procedure has been described as the operation of choice for patients with the Mirizzi syndrome type I[4]. This report reviews a series of patients who have undergone subtotal cholecystectomy over the past 5 years. The purpose of the study is to assess the results of the operation and to increase awareness of the procedure as an alternative to standard cholecystectomy or cholecystostomy.

Patients and methods

All patients who had a subtotal cholecystectomy carried out or supervised by the senior author (J.R.A.) over the 5-year period from 1986 to 1990 were included in the study. The procedure was limited to patients with severe inflammatory and/or fibrotic changes that made dissection of Calot's triangle difficult and therefore potentially dangerous, patients with portal hypertension and patients with the Mirizzi syndrome type I. All patients were followed up for a mean of 29 (range 1–62) months. *Table 1* gives details of the patients.

It is our practice to select patients for operative cholangiography on the basis of history, abnormal liver function or ultrasonography indicating either stones within the biliary tree or showing duct dilatation. Operative cholangiography was also carried out if, at the time of surgery, there were small stones within the gallbladder, if the cystic duct was found to be wide, if the common bile duct appeared dilated or if there was any problem delineating the anatomy.

Operative technique

All operations were carried out through a right subcostal or transverse incision. After division of adhesions, the area of Calot's triangle was inspected and the decision taken to perform a subtotal, rather than total, cholecystectomy. The gallbladder was opened at a convenient site, usually the fundus, and the contents were evacuated, bile being sent for culture. The gallbladder was then excised using diathermy, leaving *in situ* the wall of the gallbladder directly in contact with the liver and Calot's triangle. No attempt was made to identify the structures within this triangle.

When the cystic duct was occluded, as is often found in the Mirizzi syndrome, and where there was extensive inflammation/fibrosis, operative cholangiography was not performed. Puncture of the common bile duct is potentially dangerous and should be avoided. Postoperative endoscopic retrograde cholangiography should be carried out if visualization of the biliary tree is considered necessary in these patients.

In those patients in whom the cystic duct is patent it may be possible to dissect the duct close to its junction with the gallbladder and to carry out operative cholangiography by passing the catheter into the duct from within Hartmann's pouch, held in place by a suture surrounding the cystic duct. If this is not possible, a purse-string suture can be inserted around the opening of the cystic duct within Hartmann's pouch. Where the cystic duct is patent, it can be oversewn from within the gallbladder remnant using continuous polyglactin 910 (2/0 Vicryl®, Ethicon Ltd., Edinburgh, UK).

The gallbladder area was drained using a suction drain. All patients were given a single perioperative dose of prophylactic antibiotic (1·5 g cefuroxime) with induction of anaesthesia.

Results

Eleven patients underwent subtotal cholecystectomy during the 5-year period. This represents 3·8 per cent of the 287 patients undergoing cholecystectomy under the care of the senior author over this period. The patients can be divided into three groups on the basis of the indications for performing subtotal cholecystectomy. Six patients had severe inflammation/fibrosis. Three of these underwent urgent cholecystectomy following admission with acute cholecystitis, two were admitted for elective cholecystectomy for chronic symptoms and the final patient was admitted with jaundice, which was settling. The second group consisted of three patients with portal hypertension, and the third group comprised two patients with the Mirizzi syndrome type I.

Within the first group of six patients (see *Table 1*, patient numbers 1 to 6), imaging of the common bile duct was considered unnecessary in two. In patient number 1, endoscopic retrograde cholangiography had been carried out 3 weeks before cholecystectomy because the patient had had a raised alkaline phosphatase level and slight dilatation of the common bile duct on ultrasonography. No stones were seen within the duct system. This patient had mitral stenosis with atrial fibrillation and a past history of a cerebovascular accident. Patient number 2 was a severe asthmatic who underwent endoscopic retrograde cholangiography and endoscopic sphincterotomy for common bile duct stones. Twelve months later cholecystectomy was indicated because of continuing pain. He underwent check endoscopic retrograde cholangiography 3 weeks before cholecystectomy. Patient number 3 had previously undergone a Pólya gastrectomy for ulcer disease and presented with jaundice. A long afferent loop in this patient precluded endoscopic retrograde cholangiography. Percutan-

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Table 1 *Patient details*

No.	Sex	Age (years)	Presentation	CBD imaging	Follow-up (months)
Severe inflammation					
1	F	61	Acute on chronic cholecystitis	Preoperative ERC	Uneventful (62)
2	M	58	Acute on chronic cholecystitis	Preoperative ERC	Died from gastric carcinoma (58)
3	M	47	Jaundice	Preoperative PTC (previous Pólya gastrectomy)	CBD stone removed surgically at 21 months. Well since (35)
4	F	75	Chronic cholecystitis	Not done	Died from myocardial infarction (21)
5	F	59	Chronic cholecystitis	Not done	Uneventful (8)
6	F	41	Acute on chronic cholecystitis	Operative cholangiography	Uneventful (1)
Portal hypertension					
7	M	38	Chronic cholecystitis (portal hypertension secondary to portal vein thrombosis)	Not done	Uneventful (54)
8	F	56	Acute on chronic cholecystitis (alcoholic cirrhotic with portal hypertension)	Operative cholangiography	Uneventful (45)
9	F	59	Chronic cholecystitis (chronic active hepatitis with cirrhosis + portal hypertension)	Preoperative ERC and sphincterotomy for CBD stones	Died from variceal haemorrhage (6)
Mirizzi syndrome					
10	F	48	Jaundice	Postoperative ERC	Uneventful (24)
11	F	65	Jaundice	Postoperative ERC	Uneventful (2)

CBD, common bile duct; ERC, endoscopic retrograde cholangiography; PTC, percutaneous transhepatic cholangiography

eous transhepatic cholangiography carried out before operation had shown minimal dilatation of the common bile duct, but no stones within it. By the time of operation, this patient's jaundice had resolved. Patient number 3 remained well for 21 months following cholecystectomy (liver function tests were normal) but then became jaundiced again. Repeat percutaneous transhepatic cholangiography indicated a small stone within the common bile duct, which was removed surgically. This may represent a retained stone missed by percutaneous transhepatic cholangiography.

In the second group of patients (those with portal hypertension), operative cholangiography was considered unnecessary in one patient (patient number 7) and was carried out in one of the remaining two (patient number 8) because of a large number of small stones within the gallbladder. The third patient within this group (patient number 9) underwent endoscopic retrograde cholangiography and endoscopic sphincterotomy for common bile stones, and 18 months later underwent cholecystectomy for continuing symptoms. Operative cholangiography in this case proved impossible because of technical difficulties. Check endoscopic retrograde cholangiography after the operation indicated a lack of stones within the common bile duct. Of the patients in the second group, one (patient number 7) was Child's grade A and the others were Child's grade B. During the early part of the 5-year period, three different patients with portal hypertension (all Child's grade B) underwent a standard cholecystectomy. Of these, two required 5 units of blood owing to haemorrhage from the liver bed. Following this experience, subtotal cholecystectomy was performed in patients with portal hypertension and the problem of haemorrhage was overcome.

The remaining two patients had the Mirizzi syndrome type I. Both were minimally jaundiced with high levels of alkaline phosphatase. Preoperative ultrasonography in these patients had indicated multiple stones within the gallbladder, but no evidence of duct dilatation, although in both cases this emerged as misleading. Diagnosis of the Mirizzi syndrome was made at operation. Frozen section examination of the gallbladder was not carried out in either case. Operative cholangiography in these patients was not possible as the cystic duct lumen was obliterated, direct puncture of the common hepatic duct being considered dangerous because the anatomy was distorted. In retrospect, both patients should have undergone preoperative endoscopic retrograde cholangiography. Postoperative endoscopic retrograde cholangiography, however, confirmed the diagnosis in these patients.

Two of the 11 patients in this study developed complications following their operation, one developing a minor wound infection and the other (patient number 11) a small bile leak. This leak settled to allow removal of the suction drain on the fourth postoperative day. Neither complication delayed the patient's discharge from hospital. None of the patients required blood transfusion.

Discussion

We agree with Bornman and Terblanche that subtotal cholecystectomy is a straightforward, safe procedure in patients for whom standard cholecystectomy would have been extremely hazardous[3]. The region of Calot's triangle is the area that presents the greatest risk when carrying out a cholecystectomy, the common bile duct, common and right hepatic ducts and the right hepatic artery all being at risk of damage. Severe fibrosis associated with inflammation can also distort the anatomy in this region, increasing the risk of damage to these structures. In the Mirizzi syndrome type I, Hartmann's pouch with its contained stone is adherent to the common hepatic duct as a result of long-standing inflammation and fibrosis, and Calot's triangle is obliterated. In this case, dissection of the gallbladder from the common hepatic duct is extremely hazardous and significantly increases the risk of damage to the duct. Recently, Baer *et al.* have suggested that subtotal cholecystectomy is the treatment of choice for the Mirizzi syndrome type I[4].

Within this group of patients, imaging of the biliary tree can be problematical, as the cystic duct lumen is often obliterated. When it is patent, operative cholangiography can be carried out as described. When the cystic duct is obliterated we have often found it impossible to define the common hepatic duct and believe that direct puncture of this duct is also hazardous. In this situation we would advocate postoperative endoscopic retrograde cholangiography. In those patients who are jaundiced, preoperative imaging of the biliary tree should be carried out, either by endoscopic retrograde cholangiography or percutaneous transhepatic cholangiography depending upon the clinical circumstances and availability of the two techniques. In patients suspected before operation of having the Mirizzi syndrome, endoscopic retrograde cholangiography should be carried out.

Cholecystectomy in the presence of portal hypertension, especially secondary to cirrhosis, can be a formidable and bloody operation, increased vascularity in the region of the porta hepatis and in the free edge of the lesser omentum, limited hepatocellular function and a cirrhotic liver bed all contributing to the bleeding which can occur during this procedure. Even with correction of coagulopathy, bleeding may still be a major problem. In the present study the three patients with portal hypertension all underwent an uncomplicated operation with none requiring blood transfusion. We believe that subtotal cholecystectomy should be considered for all patients with portal hypertension. Within this group of patients, abnormalities of liver function, sometimes associated with jaundice, make it difficult to distinguish between common bile duct stones and hepatocellular disease. Although at the time of surgery it is frequently possible to cannulate the cystic duct via Hartmann's pouch, our experience argues for preoperative endoscopic retrograde cholangiography in all patients with portal hypertension and abnormal liver function with endoscopic sphincterotomy when indicated. This will overcome any difficulties which may be encountered in carrying out operative cholangiography (as occurred in one patient) and avoids the need for exploration of the common bile duct.

The time-honoured alternative to cholecystectomy in these difficult cases is generally considered to be cholecystostomy, the major disadvantages of which are well known. Welch and Malt reported retained stones in the gallbladder or common bile duct in 27 per cent of patients who survived cholecystostomy, with others reporting this condition in up to 75 per cent of patients[5]. Winkler *et al.* have reported a mortality rate of 5 per cent with cholecystostomy, but 70 per cent of their surviving patients underwent cholecystectomy 6–8 weeks later[6]. In patients in whom calculi are completely cleared at cholecystostomy, the majority will go on to form further stones and develop symptoms necessitating a second definitive operation. Fifty per cent of the recurrences take place within 3 years of the original operation[7]. During the 5-year period under review we have not carried out a cholecystostomy.

Subtotal cholecystectomy is a definitive procedure and avoids the need for a second operation. It is both safe and straightforward and should be possible to perform in the majority of cases where previously cholecystostomy had been considered.

References

1. Aranha GV, Sontag SJ, Greenlee HB. Cholecystectomy in cirrhotic patients: a formidable operation. *Am J Surg* 1982; **143**: 55–60.
2. Schwartz SI. Biliary tract surgery and cirrhosis: a critical combination. *Surgery* 1981; **90**: 577–83.
3. Bornman PC, Terblanche J. Subtotal cholecystectomy: for the difficult gall bladder in portal hypertension and cholecystitis. *Surgery* 1985; **98**: 1–6.
4. Baer HU, Matthew JB, Schweizer WP, Gertsch P, Blumgart LH. Management of the Mirizzi syndrome and the surgical implication of cholecystcholedochal fistula. *Br J Surg* 1990; **77**: 743–5.
5. Welch JP, Malt RA. Outcome of cholecystostomy. *Surg Gynecol Obstet* 1972; **135**: 717–21.
6. Winkler E, Kaplan O, Gutman M, Skornick Y, Rozin RR. Role of cholecystostomy in the management of critically ill patients suffering from acute cholecystitis. *Br J Surg* 1989; **76**: 693–5.
7. Norrby S, Schonebeck J. Long term results with cholecystolithotomy. *Acta Chir Scand* 1970; **136**: 711.

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Effect of biliary infection on common bile duct healing in the rat

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It has been postulated that biliary infection plays a role in bile duct stricture formation. The aim of this study was to verify this hypothesis and to evaluate the effect of biliary infection on common bile duct healing. A 3-mm longitudinal choledochotomy was performed in 120 rats and closed with a continuous 11/0 Ethilon® suture. Common bile duct division with end-to-end anastomosis using interrupted 11/0 Ethilon sutures was performed in another 30 rats. Biliary infection was achieved in half of the animals with retrograde injection of living 046:K1:H31 strain Escherichia coli *recovered from the rat colonic content. All rats with choledochotomy, including those with biliary infection, showed no bile leakage at the suture line, and the bursting pressure at the site of choledochotomy exceeded 40 mmHg as early as 24 h. Rats with common bile duct anastomosis alone showed no stricture formation for up to 6 months after operation. All rats with biliary sepsis developed complete occlusion at the anastomosis. On scanning electron microscopy, the biliary epithelium was well preserved in all rats. The study suggests that in rats with biliary sepsis the risk of bile leakage after primary closure of the common bile duct is negligible, but biliary infection may play a critical role in common bile duct stricture formation.*

Iatrogenic strictures of the bile duct and leakage at biliary anastomosis or closure continue to be a major clinical problem[1]. Conflicting data indicate that the pathophysiology of stricture formation is not fully understood. It is usually attributed to lack of direct mucosa-to-mucosa suturing, tension at the anastomosis, ischaemia of the bile duct, inadequate or short-term stenting, and a tissue irritating effect of bile[2-5]. The association of cholangitis with recurrent stricture has long been recognized, but few authors speculate that scar formation may be more aggressive in the presence of chronic infection[6,7].

In this study, a rat model of longitudinal choledochotomy and end-to-end anastomosis of the transected common bile duct was used to study healing of the common bile duct after retrograde intrabiliary injection of living *Escherichia coli*.

Materials and methods

Animals. Male Sprague-Dawley rats (300-350 g) were purchased from ALAB, Stockholm, Sweden, and were maintained on a standard laboratory diet (Brood Stock and Feed for Rats and Mice R3, Ewos-Anticimex, Stockholm, Sweden) and tap water *ad libitum*. Microvascular procedures were carried out under ether anaesthesia using a sterile technique and an operating microscope (ZEISS OPMI 6, Germany). The suture material used was 11/0 Ethilon® with a BV50-3 needle (Ethicon, New York, USA).

Choledochotomy. This was performed proximally to the most distal pancreatic duct. It was 3 mm long and was closed immediately with a continuous suture. The extent of common bile duct dissection was minimal to spare adjacent blood vessels.

End-to-end-common bile duct anastomosis. The common bile duct was grasped in a double clamp, divided obliquely and immediately anastomosed with eight interrupted sutures.

Bacteria. E. coli (046:K1:H31 strain) was recovered from the colonic content of the Sprague-Dawley rat. Aliquots were frozen at −80°C. Immediately before use, the bacteria were thawed and diluted in Todd-Hewitt broth to obtain 0·1 ml volumes, each containing 1×10^8 colony forming units. Characterization of *E. coli* was carried out as earlier described[8]. It produced no haemolysin. Haemagglutination was found to be negative with human, bovine, rabbit and pig erythrocytes, but positive with guinea-pig and rat erythrocytes. It was sensitive to D-mannose when the bacteria were grown at 37°C, but not at 20°C. Under similar conditions, particle agglutination was negative with fibrinogen but positive with collagen type I, fibronectin, vitronectin and laminin.

Bacterial challenge was achieved with retrograde intrabiliary injection of 1×10^8 colony forming units of living *E. coli*. The bacteria were injected at a rate of 0·2 ml/min with the aid of an infusion pump (Harvard 940A, Millis, Massachusetts, USA). Controls received intrabiliary injection of 0·1 ml saline.

Experimental design. Group Ia and Ib rats were subjected to choledochotomy alone (Ia, $n=60$) or choledochotomy and bacterial challenge (Ib, $n=60$). They were killed in batches of 12 rats after 1, 2, 4, 7 and 14 days. From each batch, nine rats were used for bile culture, measurement of common bile duct bursting pressure and light microscopy. The remaining three rats were used for bile culture and scanning electron microscopy of the common bile duct.

Group IIa and IIb rats underwent common bile duct anastomosis alone (IIa, $n=12$) or common bile duct reconstruction after bacterial challenge (IIb, $n=12$). All rats were killed after 4 weeks for evaluation of common bile duct patency and morphology (dissection under the operating microscope, light and scanning electron microscopy). Bile cultures were obtained.

Group III rats ($n=6$) underwent common bile duct anastomosis alone and were killed after 6 months for gross and microscopic analysis of common bile duct reconstruction. In addition, serum was collected for measurement of total bilirubin and alkaline phosphatase activity.

Terminal evaluation. The site of choledochotomy was isolated between two 6/0 black silk ligatures, and the distal one was secured by tubing introduced aseptically into the common bile duct lumen. Bile was taken for culture, the abdomen was filled with saline, and air was insufflated at a rate producing an increment in pressure of 1 mmHg/s (Harvard infusion pump, sphygmomanometer). Bursting pressure was recorded when the first bubbles of air appeared.

Microscopy. Light microscopy was performed on formalin-fixed 5-μm sections stained with haematoxylin and erythrosin, and van Gieson methods. Scanning electron microscopy was carried out using conventional methods: 2·5 per cent glutaraldehyde fixative, dehydration in alcohol, and Freon TF, drying by the critical point method with carbon dioxide and sputtering with a 20-nm layer of gold and palladium. Observations were made using a JEOL JSM-T 330 microscope operated at an accelerating potential of 15-20 kV.

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Results

Effects of bacterial challenge on common bile duct healing

All group Ia and Ib rats survived the experiment and at sacrifice the proximal common bile duct was not dilated. In controls (group Ia), the bursting pressure rapidly and progressively increased, exceeding 40 mmHg as early as 24 h (*Figure 1*). After 1 week, the mean bursting pressure approached 200 mmHg. Bile cultures were negative.

In rats subjected to bacterial challenge (group Ib), the bursting pressure rose rapidly, reaching almost 150 mmHg at 24 h. After another 24 h, it dropped and was then lower than in controls. At later time-points, there were no differences between the two groups. Positive bile cultures were obtained after 1, 2 and 4 days. At later time-points, the number of culture-positive rats decreased (five of nine after 7 days; one of nine after 14 days).

In rats subjected to bacterial challenge, the site of choledochotomy was, as evident from light microscopy, severely inflamed with abscesses and necrotic lesions seen in the adjacent pancreatic tissue. In contrast, group Ia controls showed much less inflammation, with microabscesses seen only in some sections.

On scanning electron microscopy, the biliary epithelium was well preserved in all rats (*Figure 2*) and lined the duct wound by day 4. During infection, numerous inflammatory cells accumulated at the suture line (*Figure 3*).

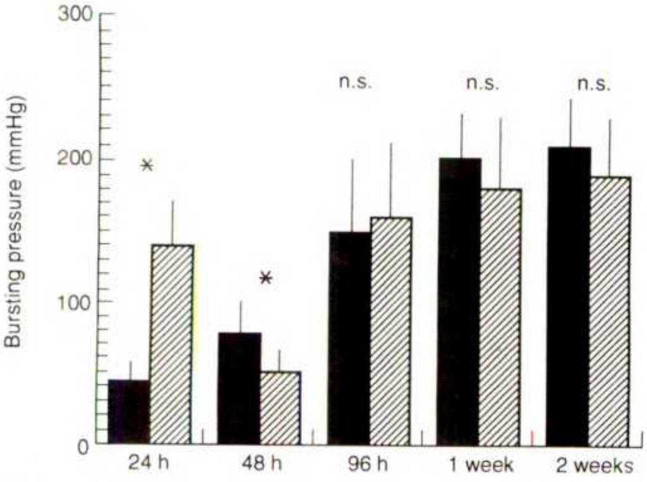

Figure 1 *Results of bursting pressure measurements at the site of choledochotomy. ■, Controls; ▨, infected. *Probability of random difference of* $P < 0.01$ *as determined by Student's* t *test; n.s., not significant*

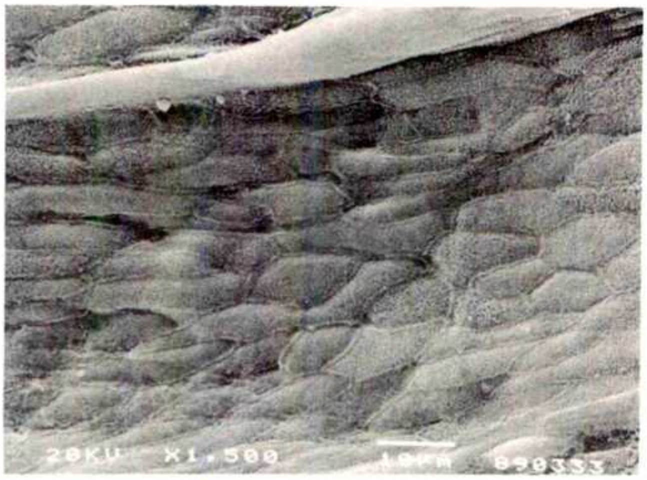

Figure 2 *Biliary epithelium was well preserved in all rats, indicating that dissection of the common bile duct did not impair its blood supply (scanning electron microscopy 24 h after choledochotomy alone, original magnification × 1500)*

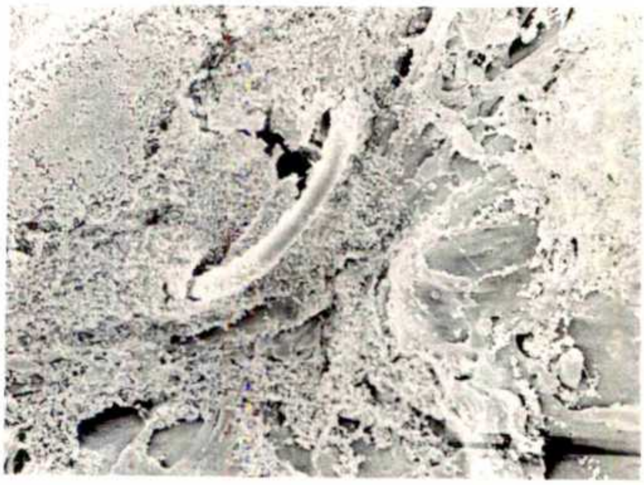

Figure 3 *In rats with biliary sepsis numerous macrophages accumulated at the site of choledochotomy (scanning electron microscopy 48 h after operation, original magnification × 100)*

Effect of bacterial challenge on common bile duct anastomosis

All group II and III rats survived the experiment. After 4 weeks, both the controls (group IIa) and group III rats showed no stricture formation. In addition, group III rats displayed normal serum bilirubin and alkaline phosphatase activity. All infected rats (group IIb) developed complete occlusion at the anastomosis. The proximal common bile duct was greatly dilated and contained chylous pus from which *E. coli*, *Streptococcus faecalis* and *Bacteroides fragilis* were isolated.

Discussion

A rat model of longitudinal choledochotomy and end-to-end common bile duct anastomosis was found to be reliable, reproducible, and associated with neither mortality nor morbidity. Dissection of the common bile duct did not damage the biliary epithelium as demonstrated by scanning electron microscopy. *E. coli* used in this study was shown to be tissue-invasive, and retrobiliary injection produced a 100 per cent yield of early biliary sepsis.

In normal rats, the risk of bile leakage after primary closure of a choledochotomy is negligible because as early as 24 h the pressure needed to disrupt the suture line was more than 40 mmHg. Although the mean bursting pressure in rats with biliary infection was (at 48 h) lower than in controls, it was still above 50 mmHg. Bile infection did not increase the risk of bile leakage. In parallel experiments evaluating the effect of bile flow on common bile duct repair, it was found that bile accelerated wound healing, presumably through induction of a local inflammatory response. The present data support this hypothesis, because rats with biliary infection required exceptionally high bursting pressure values (at 24 h) which were associated with severe local inflammatory reactions. A transient drop in bursting pressure observed at 48 h was probably caused by an increased infiltration with neutrophils.

Without stenting, non-infected rats subjected to microsurgical common bile duct reconstruction showed excellent healing with no tendency to stricture formation, whereas those with biliary sepsis developed complete occlusion at the anastomosis. Some suggest that stricture formation may be more aggressive in the presence of infection[6,7]. This study provides evidence that biliary sepsis is of critical importance.

We have shown that many different bacteria, including the *E. coli* strain used in this study, may colonize traumatized connective tissues and blood clots in wounds by binding to fibrinogen, fibrin, fibronectin, laminin and collagen[9,10]. This in turn enhances local inflammatory reaction with accumulation of cells known to promote fibrosis[11].

A patient undergoing biliary reconstruction is usually infected or is at high risk of biliary sepsis from drainage[12,13]. The worst results are seen after end-to-end bile duct anastomosis where additional factors such as duct ischaemia, tension at the anastomosis and imperfect surgical technique act in concert[3–6,14–16].

In the colon of rats as well as humans there are several different strains of *E. coli*. Some are tissue-invasive like the 046:K1:H31 strain used in this study. Others might be less invasive or even 'innocent'. It is, therefore, conceivable that the outcome of biliary reconstruction might be dependent on the type of bacteria present in the bile. Traditionally, internal stenting is thought to prevent stricturing[14], although some authorities advocate a no-tube technique[17]. The latter seems to be supported by experimental evidence[5,18–20] and, as shown in this study, secondary stent-related biliary infection is likely to increase the risk of (re)stenosis.

In summary, primary closure of the choledochotomy in rats is not associated with bile leakage, because healing of the common bile duct occurs rapidly, even with concurrent biliary sepsis. Under aseptic conditions, microsurgical common bile duct reconstruction does not require stenting. It is followed by prompt healing without a tendency towards stricture formation. In contrast, all common bile ducts infected with tissue-invasive strains of *E. coli* become obstructed at the anastomosis. Biliary infection plays a critical role in the pathogenesis of common bile duct stricture formation.

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References

1. Johnston GW. Iatrogenic bile duct stricture: an avoidable surgical hazard? *Br J Surg* 1986; **73**: 245–7.
2. Cattell RB, Braasch JW. Primary repair of benign strictures of the bile duct. *Surg Gynecol Obstet* 1959; **109**: 531–8.
3. Thomas JP, Metropol HJ, Myers RT. Teflon patch graft for reconstruction of the extrahepatic bile ducts. *Ann Surg* 1964; **160**: 967–70.
4. Northover JMA, Hickman R, Watson RGK, Terblanche J. Healing of the bile duct anastomosis after transverse choledochotomy or transplantation of the liver in the pig. *Surg Gynecol Obstet* 1985; **160**: 33–6.
5. Rand RW, Cannon JA, Rodriguez RS. Microsurgery of the common bile duct. An experimental and clinical study. *Am J Surg* 1970; **120**: 215–21.
6. Goswitz JT, Macpherson CR, Elliott DW. Experimental investigation of secondary biliary strictures. *Am J Surg* 1963; **105**: 221–7.
7. Hertzer NR, Gray HW, Hoerr SO, Hermann RE. Use of T-tube splints in duct repairs. *Surg Gynecol Obstet* 1973; **137**: 413–18.
8. Naidu AS, Paulsson M, Wadström T. Particle agglutination assays for rapid detection of fibronectin, fibrinogen, and collagen receptors on *Staphylococcus aureus*. *J Clin Microbiol* 1988; **26**: 1549–54.
9. Speziale P, Hook M, Wadström T, Timpl R. Binding of the basement membrane protein laminin to *Escherichia coli*. *FEBS Lett* 1982; **146**: 55–8.
10. Wadström T, Speziale P, Rozgonyi F, Ljung Å, Maxe I, Ryden C. Interactions of coagulase negative staphylococci with fibronectin and collagen as possible first step of tissue colonization in wounds and other tissue trauma. *Zentralbl Bakteriol Mikrobiol Hyg Ser* 1987; **A16**: 83–91.
11. Hunt TK, Knighton DR, Thakral KK, Goodson WH III, Andrew WS. Studies on inflammation in wound healing: angiogenesis and collagen synthesis stimulation *in vivo* by resident and activated wound macrophages. *Surgery* 1984; **96**: 48–54.
12. Audisio RA, Bozzetti F, Severini A *et al.* The occurrence of cholangitis after percutaneous biliary drainage: evaluation of some risk factors. *Surgery* 1988; **103**: 507–12.
13. Keighley MRB, Lister DM, Jacobs S, Giles GR. Hazards of surgical treatment due to microorganisms in the bile. *Surgery* 1974; **75**: 578–83.
14. Warren KW, Jefferson MF. Prevention and repair of strictures of the extrahepatic bile ducts. *Surg Clin North Am* 1973; **53**: 1169–90.
15. Lahey FH, Pyrtek LJ. Experience with the operative management of 280 strictures of the bile ducts with description of a new method and a complete follow-up study of end results in 299 of the cases. *Surg Gynecol Obstet* 1950; **91**: 25–56.
16. Smith R. Obstructions of the bile duct. *Br J Surg* 1979; **66**: 69–79.
17. Bismuth H, Franco D, Corlette MB, Hepp J. Long term results of Roux-en-Y hepatico-jejunostomy. *Surg Gynecol Obstet* 1978; **146**: 161–7.
18. Lary BG, Scheibe JR. The effect of rubber tubing on the healing of common duct anastomosis. *Surgery* 1952; **32**: 789–95.
19. Casey WJ, Peacock EE. Some factors affecting pathophysiology of bile duct stenosis. *Surg Forum* 1977; **28**: 414–16.
20. Lamesch AJ, Dociu N. Microsurgical reconstruction of the biliary duct: experimental study in rats and dogs. *Microsurgery* 1986; **7**: 46–52.

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Treatment perspectives in locally advanced unresectable pancreatic cancer

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Locally advanced unresectable pancreatic cancer is sometimes encountered without manifest distant metastases. Twenty patients with histologically proven unresectable pancreatic cancer without distant metastases were treated with radiotherapy and 5-fluorouracil (5-FU). Radiotherapy consisted of 50 Gy external upper abdomen radiation in two courses, concomitant with intravenous 5-FU 375 mg/m^2 given as a bolus injection 4–6 h before radiation on the first 4 days of each treatment course. The treatment protocol was completed in 18 patients without complications. The median survival time was 10 months which compares favourably with a 3–5 months median survival time when treatment is withheld. Nine patients (45 per cent) were alive at 1 year, two patients at 2, 3 and 4 years. A second-look operation was performed in four patients 6, 11, 12 and 22 months after completion of radiotherapy. In two patients the tumour could be resected. It appears that treatment with radiotherapy and 5-FU may benefit patients with locally advanced unresectable pancreatic cancer.

Pancreatic cancer has a dismal prognosis, with a 5-year survival rate of between zero and 15 per cent after resection. In spite of the development of advanced diagnostic procedures, most patients will have locally advanced disease or distant metastases at the time of diagnosis. In some series distant metastases and locally advanced disease are found at laparotomy in 60–70 per cent of cases considered potentially resectable.

In cases of locally advanced cancer, distant metastases may be absent. It should be stressed that it may be extremely difficult to assess accurately before, and even during, laparotomy whether the tumour arises in the pancreas or periampullary region, and whether invasion of surrounding organs is caused by an inflammatory reaction or tumour infiltration. Treatment is usually withheld from those patients in whom surgical resection is not possible. In other locally invasive digestive tract cancers, such as colonic and gastric cancer, distant metastases are not necessarily present and cure can be obtained by adequate local treatment[1–4].

Since 1982 we have offered treatment with local radiotherapy combined with 5-fluorouracil (5-FU) to patients with proven unresectable localized pancreatic cancer without signs of distant metastases. The value of this combined treatment was suggested by results of the Gastrointestinal Tumor Study Group (GITSG), which showed better results if 5-FU was combined with radiation therapy[5,6]. The results of this treatment appear to be promising, offering the patient the opportunity for long-term survival.

Patients and methods

Between May 1982 and January 1990, 206 patients were operated on for pancreatic and periampullary cancer at the University Hospital Dijkzigt, Rotterdam. Pancreatic resection was performed in 108 patients. Twenty of the remaining 98 patients had locally advanced unresectable pancreatic cancer without metastases and were treated with combined radiotherapy and 5-FU. In 19 patients irresectability was established at operation. An endoprosthesis was left *in situ* for drainage of bile in eight patients. A choledochojejunostomy was performed in only five patients and a gastrojejunostomy in six patients. The diagnosis was confirmed by pathological examination in all 20 patients. Radiotherapy and 5-FU treatment were performed in the Dr Daniël den Hoed Cancer Center, Rotterdam. Radiotherapy was given according to a protocol consisting of a total of 50 Gy external radiation in two couses with intravenous 5-FU 375 mg/m^2 given as a bolus injection 4–6 h before radiation on the first 4 days of each treatment course. The daily fraction of radiation was 2 Gy. The interval between the two courses was 3 weeks. Radiation technique involved multiple-field treatment planning using computed tomography. Megavolt energy of 25 MV was preferred, although occasionally 4, 6 or 8 MV was used. The main concern was protection of the kidneys and spinal column. Technical details of the radiotherapy protocol are described by Treurniet-Donker *et al.*[7]. This protocol was developed on the basis of the results of GITSG[5–8].

The choice of radiation dose of 50 Gy was a compromise between the 40 and 60 Gy doses used in the GITSG study. In order to limit treatment duration in this group of patients with such a limited survival we decided not to give the maintenance 5-FU as used in the GITSG study. In using the dose of 50 Gy in fractions of 2 Gy, actual treatment time was limited to 5 weeks. Half way through this treatment a pause of 3 weeks was considered valuable to allow acute reactions to therapy to subside.

Irresectability of the tumour was established during laparotomy when tumour invasion was considered to be present in the hepatoduodenal ligament, in adjacent peritoneum, in the transverse mesocolon, or in a large part of the superior mesenteric vein and/or portal vein. Histopathological confirmation of adenocarcinoma in the pancreas was obtained in all cases. Differentiation between pancreatic duct cancer or periampullary cancer was not possible in these cases. For such a diagnosis, resection specimens are necessary, with information about the exact position of the tumour.

The tumour node metastasis (TNM) cancer classification was used with a modification for the N stage. The N_{1a} stage was denoted as a situation in which local peripancreatic lymph nodes contained tumour, whereas regional and distant lymph nodes were free of tumour. N_{1b} indicated the presence of distant lymph node metastases. The TNM staging procedure is depicted in *Table 1*.

In total, 20 patients with histologically proven adenocarcinoma in the pancreas ($T_3N_{0-2}M_0$) were treated with radiotherapy and 5-FU. The treatment protocol could be completed in 18 patients. In one patient, radiotherapy treatment was discontinued after 34 Gy because of a deterioration in general condition. In one patient, 5-FU treatment was discontinued during the second course due to leucopenia. In four patients, a second-look operation was performed 6, 11, 12 and 22 months, respectively, after treatment with radiotherapy and 5-FU. Resection of the pancreas was possible in two of these patients.

Survival was calculated from the date of surgery until May 1991, on an actuarial basis using the Kaplan–Meier method. Death from disease was taken as the endpoint in the study.

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Table 1 *TNM classification for pancreatic carcinoma*

Stage	Description
T (primary tumour)	
T_x	Primary tumour cannot be assessed
T_0	No evidence of primary tumour
T_1	Tumour limited to the pancreas
	T_{1a}, tumour 2 cm or less in greatest dimension
	T_{1b}, tumour more than 2 cm in greatest dimension
T_2	Tumour extends directly to the duodenum, bile duct or peripancreatic tissues, still enabling resection
T_3	Tumour extends directly to the stomach, spleen, colon or adjacent large vessels, not enabling resection
N (regional lymph nodes)	
N_x	Regional lymph nodes cannot be assessed
N_0	No regional lymph node metastasis
N_1	Lymph node metastasis
	N_{1a}, locally in resection specimen
	N_{1b}, lymph node metastasis regionally outside the resection area
M (distant metastasis)	
M_x	Presence of distant metastasis cannot be assessed
M_0	No distant metastasis
M_1	Distant metastasis

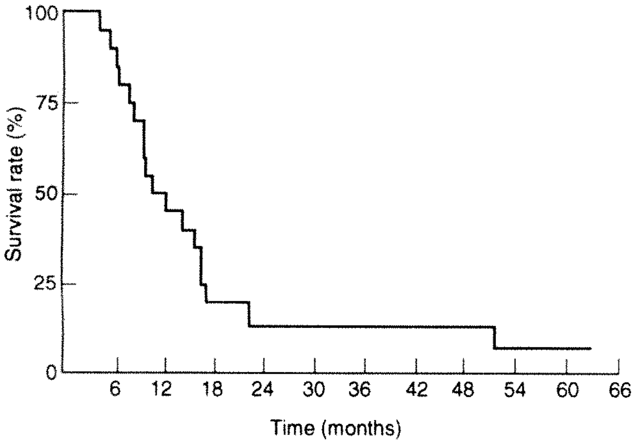

Figure 1 *Survival from time of diagnosis at laparotomy of 20 patients with locally unresectable pancreatic cancer treated with radiotherapy and 5-fluorouracil. One patient survived for more than 5 years. All patients were followed for at least 16 months*

Results

There were no deaths related to surgery or to treatment with radiotherapy and 5-FU. The treatment protocol was completed in a total of 18 patients without complications. Jaundice occurred in four patients with an endoprosthesis. This was successfully treated by replacement of the endoprosthesis. Reoperation for bile duct obstruction or duodenal obstruction was not necessary in any case. At 1 year, nine (45 per cent) patients were alive. Two patients survived for 2 years and were still alive at 4 years. One patient is alive more than 5 years after diagnosis, but has signs of metastases in the lung (*Figure 1*).

A second-look operation was carried out in four patients at 6, 11, 12 and 22 months after completion of radiotherapy in order to resect the tumour remnant. These patients did not have signs of progressive disease and were in good condition. Resection was possible in two of these patients who originally had an irresectable pancreatic cancer. In the other two patients the tumour was still unresectable.

Pathological investigation after resection in one of these patients showed a small pancreatic ductal adenocarcinoma measuring 0·5 cm in the head of the pancreas without evidence of lymph node metastases. In the other patient the tumour invaded the duodenum, and local peripancreatic lymph node metastases were found. There were no postoperative complications. The two patients who underwent resection are still alive, although one is the 5-year survivor who now has distant metastases.

Discussion

Cure in patients with pancreatic cancer is obtained in only a small percentage of cases, even when a so-called curative resection can be carried out. This has led to a pessimistic approach towards the operative treatment of this condition. At laparotomy the cancer often appears to be inoperable due to metastases or locally advanced disease. At this stage the tumour is generally regarded as incurable and treatment is withheld. This approach can be challenged in patients with locally advanced disease who have no signs of distant metastases.

Comparable situations with other carcinomas such as gastric and colonic cancer indicate that tumour growth into surrounding tissue can indeed occur without the occurrence of distant metastases. *En bloc* resection of such locally advanced cancers can lead to long-term survival[1–4]. In locally advanced pancreatic cancer, *en bloc* resection is not possible because of the anatomical position of the pancreas. We have treated these irresectable tumours with radiotherapy and 5-FU. Treatment was generally well tolerated and was completed in 18 of 20 patients.

The survival rate was 45 per cent at 1 year, and 13 per cent at 2, 3 and 4 years. Median survival time was 10 months. Presently, one patient is alive at more than 5 years after treatment. Other investigators have found a median survival of 9–12·5 months after combined radiotherapy and chemotherapy in locally unresectable pancreatic cancer[5–14], which compares favourably with a median survival of 3–5 months when treatment is withheld. There are reports[7,8] of 5-year survival after combined treatment with radiotherapy and 5-FU. Survival in our study after treatment with radiotherapy and 5-FU was similar to that of patients with resectable cancer. The median survival time after 'curative' pancreatic resection for pancreatic cancer is, in our experience, 13·3 months in 50 patients; 1-year and 4-year survival rates are 56 and 11 per cent, respectively. This surprising finding may be explained by the assumption that the tumour stage of patients with resectable tumours is similar to this selected group of patients with advanced unresectable cancer but no distant metastases.

It is known in colonic cancer that about 40 per cent of adjacent organ involvement appears to be inflammatory. These data are not available for locally invasive pancreatic cancer because resection specimens are not available. In this study, invasion of the tumour into surrounding tissues was usually diagnosed by macroscopic examination during laparotomy. Thus, it may be that some of our patients did not have tumour infiltration, but only inflammatory infiltration around the tumour as a result of pancreatitis, which might explain the favourable survival rate. This is a further reason not to withhold treatment when the tumour appears to be unresectable. It also emphasizes the point that pathological confirmation of carcinoma must be established in order to exclude pancreatitis of the head of the pancreas mimicking a carcinoma.

It was our policy to avoid bypass operations during the exploratory laparotomy unless there was obstruction of the bile duct or gastric outlet, because preventive bypass surgery may lead to unnecessary complications and mortality. A reoperation for obstructive symptoms was not necessary in any of the 20 patients.

The value of a second-look operation in these patients is shown by the possibility of resection in two of our four patients who had this procedure. The tumour was still present but had reduced to a resectable size. Second-look operations have also been described by Pilepich and Miller[15]. They were able to perform resection in six patients after preoperative radiation; two of these six patients were still alive after 5 years.

We conclude that treatment with radiotherapy and 5-FU in patients with locally advanced irresectable cancer of the pancreas can be achieved with little morbidity and may offer longer survival.

References

1. Papachristou DN, Shiu MH. Management by *en bloc* multiple organ resection of carcinoma of the stomach invading adjacent organs. *Surg Gynecol Obstet* 1988; **152**: 483–7.
2. Viste A, Lillestøl J, Søreide O. Cancer of the stomach: are curative resections of any importance with respect to postoperative survival in patients with locoregional disease? *Int Surg* 1984; **69**: 133–5.
3. Kroneman H, Castelein A, Jeekel J. *En bloc* resection of colon carcinoma adherent to other organs: an efficacious treatment? *Dis Colon Rectum* (in press).
4. Bonfanti G, Bozzetti F, Doci R *et al.* Results of extended surgery for cancer of the rectum and sigmoid. *Br J Surg* 1982; **69**: 305–7.
5. The Gastrointestinal Tumor Study Group. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil. *Cancer* 1981; **48**: 1705–10.
6. The Gastrointestinal Tumor Study Group. A multi-institutional comparative trial of radiation therapy alone and in combination with 5-fluorouracil for locally unresectable pancreatic carcinoma. *Ann Surg* 1979; **189**: 205–8.
7. Treurniet-Donker AD, van Mierlo MJM, van Putten WLJ. Localized unresectable pancreatic cancer. *Int J Radiat Oncol Biol Phys* 1990; **18**: 59–62.
8. Dobelbower RR, Borgelt BB, Suntharalingam N, Strubler KA. Pancreatic carcinoma treated with high-dose small-volume irradiation. *Cancer* 1978; **41**: 1087–97.
9. Falk RE, Moffat FL, Lawler M, Heine J, Makowka L, Falk JA. Combination therapy for resectable and unresectable adenocarcinoma of the pancreas. *Cancer* 1986; **57**: 685–8.
10. Selch MT, Parker RG. Results in the management of locally unresected pancreatic carcinoma. *Am J Clin Oncol* 1986; **9**: 139–45.
11. Mohiuddin M, Cantor RJ, Bierman W, Weiss SM, Barbot D, Rosato FE. Combined modality treatment of localized unresectable adenocarcinoma of the pancreas. *Int J Radiat Oncol Biol Phys* 1988; **14**: 79–84.
12. Whittington R, Solin L, Mohiuddin M *et al.* Multimodality therapy of localized unresectable pancreatic adenocarcinoma. *Cancer* 1984; **54**: 1991–8.
13. Battle Haslam J, Cavanough PJ, Stroup SL. Radiation therapy in the treatment of irresectable adenocarcinoma of the pancreas. *Cancer* 1973; **32**: 1341–5.
14. McCracken JD, Ray P, Heilbrun L *et al.* 5-Fluorouracil, methyl-CCNU, and radiotherapy with or without testolactone for localized adenocarcinoma of the exocrine pancreas. A Southwest Oncology Group Study. *Cancer* 1980; **46**: 1518–22.
15. Pilepich MV, Miller HH. Preoperative irradiation in carcinoma of the pancreas. *Cancer* 1989; **46**: 1945–9.

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Postgastrectomy osteoporosis

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Osteoporosis is a recognized complication following partial gastrectomy and is more common than osteomalacia. Recent improvements in the measurement of bone mineral status (dual energy X-ray absorptiometry, DEXA) have assisted in measuring osteoporosis. Sixteen men who had undergone gastrectomy more than 30 years previously were examined. This study reports the effect of calcium supplementation in six patients in whom osteomalacia had been excluded and who showed abnormally low bone mineral densities on DEXA scanning. Calcium supplementation for 6 months (microcrystalline hydroxyapatite, Ossopan® 8–32 g per day) produced no significant advantage for the treatment group at any site measured.

The term 'postgastrectomy bone disease' was coined because disorders in calcification of bones after gastrectomy were often the result of a combination of osteomalacia and osteoporosis[1]. In many of the earlier studies there was no differentiation between the two causes. There is increasing evidence that the incidence of osteomalacia is not high overall and that osteoporosis in excess of normal ageing is a bigger problem[2–7]. Following gastrectomy, there is an earlier onset of osteoporosis in postmenopausal women and also an acceleration in both sexes in the later osteoporosis related to ageing[6,8].

Impaired calcium absorption and increased bone resorption are two important factors in osteoporosis. Calcium absorption is impaired following gastrectomy[9], so it might be expected that increased calcium intake could be useful either in the prevention or the treatment of postgastrectomy osteoporosis.

The value of calcium supplementation in postmenopausal or senile osteoporosis is uncertain. Some studies suggest that it may be preventive[10–17], others that it is of no value in prevention[18–21]. Once osteoporosis has developed, the changes seem irreversible[11,22–25]; calcium supplementation may reduce further bone resorption according to some and not to others, but does not increase the accretion of bone.

However, there is evidence that calcium supplementation in the form of microcrystalline hydroxyapatite (MCHC; Ossopan®, Sanofi Pharma, Manchester, UK) may prevent or reduce the progress of osteoporosis in certain conditions. This paper reports the findings of a trial of MCHC in the treatment of patients who had undergone gastrectomy with evidence of osteoporosis in excess of that expected for their age as shown by dual energy X-ray absorptiometry (DEXA).

Patients and methods

Fifty-two of an original series of 227 patients[7,26] who underwent gastrectomy at University College Hospital, London between 1955 and 1960 were still attending the long-term follow-up clinic. Sixteen of these were men between the ages of 50 and 72 years who were still leading active, normal lives and were available for study. They all had steady plasma calcium, phosphate and alkaline phosphatase concentrations with no evidence of subclinical osteomalacia[7] throughout the follow-up period of 25–30 years.

DEXA is a simple technique which uses a small X-ray source and detector arrangement to determine the amount of bone mineral in the path of the X-ray beam. The results are expressed as bone mineral density in grams per centimetre squared. Whilst it is not a true density (which would be expressed as g/cm^3), more than 20 years of research with dual photon absorptiometry has shown that it gives accurate and reproducible results.

In this study, each subject had a measurement of bone mineral density of the lumbar spine (L1–L4) and left upper femur at each visit using a Hologic QDR 1000 apparatus (Hologic Incorporated, Waltham, Massachusetts, USA).

The coefficient of variation from the lumbar spine measurement was 0·9 per cent, for the femoral neck 1·2 per cent, and that for Ward's triangle 2·7 per cent. There was no drift in the results over 1 year as shown by daily phantom studies. The effective radiation dose for two bone density scans is of the order of 6–7 μSv[27].

At the initial scan, six patients were found to have a bone mineral density two standard deviations below the normal for their age. There is no definite level of bone density below which the diagnosis of osteoporosis is mandatory, so the level of 2 s.d. below the mean for the age was taken as an arbitrary guide of abnormality. This is the cut-off point most commonly used in densitometry studies. This group was given MCHC in doses varying from 16 to 32 g per day according to tolerance, for 6 months. In addition they were given a small dose of calciferol, 0·25 mg (10000 units) daily, to improve calcium absorption.

A dietary survey was done on all six patients to estimate their mean daily calcium intake. Plasma calcium, phosphate and plasma alkaline phosphatase concentrations were estimated initially and at 2-monthly intervals. The remaining ten patients with normal bone mineral density also had a dietary survey at the onset and calcium, phosphate and alkaline phosphatase estimations initially and at 6 and 12 months. Repeat spinal and femoral density assessments were made at 6 and 12 months in all patients.

The results of the femoral scan can be expressed in several ways. The femoral neck and Ward's triangle are the regions used in this study, because they are clinically relevant. Ward's triangle is a physiological region representing the area of lowest bone density within the femoral neck; this is chosen automatically by the computer.

Results

There were no significant differences in the mean or individual plasma calcium and phosphate concentrations between the treated or untreated patients or between the initial and later estimations through the 1-year period (*Table 1*).

One patient in the MCHC group had a raised plasma alkaline phosphatase concentration initially and at 6 months. Isoenzyme electrophoresis showed this to be of hepatic origin and this patient was excluded from analysis of alkaline phosphatase changes. In both groups of patients there was a significant rise in plasma alkaline phosphatase concentrations at 6 months (midwinter), although the values were still within the normal range. The initial alkaline phosphatase concentrations were also higher ($P<0·05$) in the treatment group, although within the normal range and of no clinical significance.

The dietary intake of calcium over a 1-week period was similar in both groups, the mean(s.d.) intake of calcium being 999(394) and 719(277) mg/day in the treatment and control groups respectively.

MCHC was given in powder or tablet form, whichever was more acceptable to each patient. Initially a large dose of 32 g/day was prescribed, which equates with taking 8 × 5 ml powder or 32 tablets a day. Three patients found this quantity excessive and unpalatable, and opted for a smaller dose (16 g/day). One patient started with 32 g/day and after 4 months

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Table 1 *Biochemical changes in patients treated with microcrystalline hydroxyapatite and untreated controls*

	Initial	6 months	12 months
Plasma calcium (2·20–2·60 mmol/l)*			
Treated	2·34(0·087)	2·32(0·079)	2·25(0·028)
Untreated	2·35(0·108)	2·32(0·109)	2·31(0·096)
Plasma phosphate (0·7–1·5 mmol/l)*			
Treated	0·938(0·1073)	0·945(0·2119)	1·00(0·121)
Untreated	0·816(0·1274)	0·916(0·1693)	0·8656(0·1487)
Plasma alkaline phosphatase (100–280 units/l)*			
Treated	187(38·8)	225(61·9)	192(42·4)
Untreated	137(55·3)	165(43·4)	147(30·3)

Values are mean(s.d.). *Normal range. Statistical analysis (1) treated *versus* untreated (Mann–Whitney *U* test): accept the null hypothesis in all cases except alkaline phosphatase where $P<0{\cdot}05$; (2) initial *versus* 6 months *versus* 12 months (paired *t* test): no significant difference except for alkaline phosphatase where treated initial *versus* 6 months $P<0{\cdot}05$, untreated initial *versus* 6 months $P<0{\cdot}01$, untreated 6 months *versus* 12 months $P<0{\cdot}01$

changed to 8 g/day (*see* below). The remaining five patients all received 2–4 times the recommended dose of MCHC, with a total calcium intake greater than 3 g/day.

The mean(s.d.) total combined dietary and MCHC calcium intake was 4600(1103) mg/day during the first 4 months and 3863(1383) mg/day during the last 2 months of the treatment period.

MCHC caused side-effects in two patients. One patient had mild constipation and another complained of epigastric pain when taking 32 g/day; the pain lessened when the dose was reduced to 8 g/day after 4 months and settled completely when the MCHC was discontinued at the end of the 6-month course.

The percentage changes in bone density of the lumbar spine (L1–L4) over the 12-month period in the treated and untreated groups are shown in *Figure 1*. The graphs for the changes in Ward's triangle and the femoral neck were similar. There was no consistent change in either group throughout the period.

It was concluded that even large doses of MCHC did not affect the loss of bone density over a 6-month period, nor was there any deterioration during the 6-month period after the MCHC was discontinued.

Discussion

MCHC has been reported to prevent or reduce the progress of osteoporosis in patients receiving corticosteroids and in those with juvenile idiopathic osteoporosis[28–31]. MCHC improved the calcium balance in osteogenesis imperfecta[32] and reduced bone loss in patients with Colles' fracture[33]. When given with vitamin D, MCHC resulted in partial remission of osteoporosis resistant to calcium gluconate and vitamin D in patients with primary biliary cirrhosis[34].

In animal experiments, MCHC has been shown to improve bone healing when given orally[35] and to increase new bone formation when implanted[36,37]. It has been shown to increase DNA and collagen formation in a culture of bone cells[38], and to induce differentiation of mesenchymal cells into cartilage and bone[37]. It is suggested that MCHC contains a growth factor which stimulates osteoprogenitor cells.

In a previous trial at University College Hospital in 1982, 91 patients who had undergone gastrectomy and having a low Exton-Smith index of the right second metacarpal[39] were treated with the standard dose of 8 g MCHC daily for 1 year. There was no apparent improvement in the index but the results were inconclusive because of inaccuracies due to observer error.

The present study was devised when DEXA became available. This technique permitted more accurate measurements of bone mineral content. In view of the apparent lack of response previously to the standard dose of 8 g MCHC daily, it was planned to give a larger dose limited only by the patient's tolerance and compliance. To enhance intestinal calcium absorption and transport an additional small daily dose of calciferol was given. The patients selected had been screened at least annually over 25–30 years for changes in plasma calcium, phosphate and alkaline phosphatase levels. There was no evidence of vitamin D deficiency in these patients, which made it unlikely that any changes in bone density could be related to osteomalacia.

In our previous study[26], patients with vitamin D deficiency and subclinical osteomalacia had rising plasma alkaline phosphatase levels, well above the normal range. In the present study there was no fall during treatment in the slight increase in the plasma alkaline phosphatase levels (although still within the normal range), so the elevation was unlikely to be due to vitamin D deficiency.

The results suggest that calcium supplementation, even in the form of MCHC, has no effect on postgastrectomy osteoporosis.

Attention has been drawn[7,26,40] to the increasing

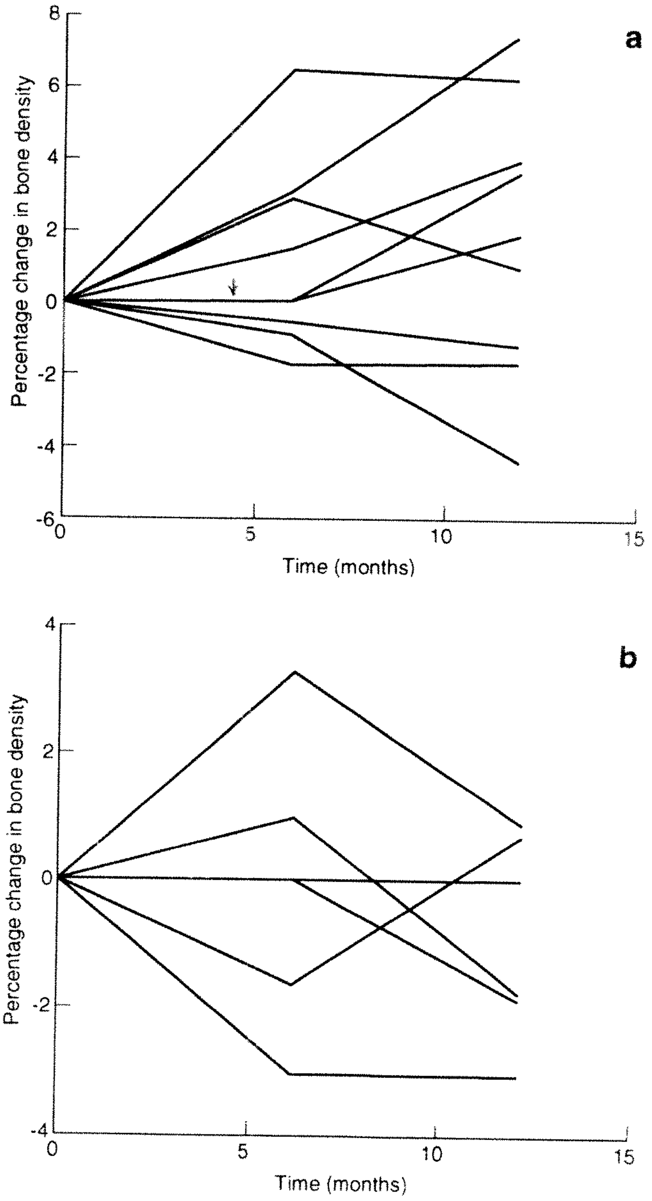

Figure 1 *Percentage changes in bone density of the lumbar spine (L1–L4).* **a** *Ten untreated patients with normal bone density. Arrow, line representing three patients, one lost to follow-up after 6 months;* **b** *six patients with low bone density treated with microcrystalline hydroxyapatite*

importance of regular screening of ageing patients who have undergone gastrectomy for evidence of subclinical osteomalacia, with the knowledge that the process can be corrected by small doses of vitamin D and calcium. Osteoporosis in excess of normal ageing for men and women is an even greater problem in these patients than osteomalacia, and, as screening facilities for osteoporosis become more generally available, patients undergoing gastrectomy should be regarded as forming a population at particular risk. Unfortunately at the moment there are no certain measures for either the prevention or treatment of osteoporosis following gastrectomy. In this report no apparent benefit was found from treatment with MCHC as shown by serial bone mineral measurements. Other new treatments such as etidronate or calcitonin need to be evaluated, and it is hoped that eventually the same success may be obtained as in the management of osteomalacia.

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References

1. Editorial. Bone disease after gastrectomy. *Br Med J* 1972; **i**: 461.
2. Deller DJ, Begley MD. Calcium metabolism and bones after partial gastrectomy: I. Clinical features and radiology of the bones. *Aust Ann Med* 1963; **12**: 282–94.
3. Deller DJ, Edwards RG, Addison M. Calcium metabolism and bones after partial gastrectomy: II. Nature and cause of the bone disorder. *Aust Ann Med* 1963; **12**: 295–309.
4. Deller DJ, Begley MD, Edwards RG, Addison M. Metabolic effects of partial gastrectomy with special reference to calcium and folic acid. Part I. Changes in calcium metabolism and the bones. *Gut* 1964; **5**: 218–25.
5. Morgan DB, Pulvertaft CN, Fourman P. Effects of age on the loss of bone after gastric surgery. *Lancet* 1966; **ii**: 772–3.
6. Rao SD, Kleinekoper M, Rogers M, Frame B, Parfitt AM. Is gastrectomy a risk factor for osteoporosis? In: Christiansen C, Arnaud CD, Nordin BEC, Parfitt AM, Peck WA, Riggs BL, eds. *Osteoporosis: Proceedings of the Copenhagen International Symposium on Osteoporosis* 1984; **2**: 775–7.
7. Tovey FI, Godfrey JE, Lewin MR. A gastrectomy population: 25–30 years on. *Postgrad Med J* 1990; **66**: 450–6.
8. Chesnut CH, Baylink DJ, Roos BA *et al.* Calcitonin and postmenopausal osteoporosis. In: Pecile A, ed. *Calcitonin 1980. Chemistry, Pharmacology and Clinical Aspects.* Amsterdam: Excerpta Medica, 1981: 247–55.
9. Nicolaysen R, Ragard K. Calcium and phosphorus metabolism in gastrectomised patients. *Scand J Clin Lab Invest* 1955; **7**: 298–9.
10. Riggs BL, Hodgson SF, Hoffman DL, Kelly PJ, Johnson KA, Taves D. Treatment of primary osteoporosis with fluoride and calcium: clinical tolerance and fracture occurrence. *JAMA* 1980; **243**: 446–9.
11. Recker RR, Savill PD, Heaney RP. Effect of oestrogens and calcium carbonate on bone loss in postmenopausal women. *Ann Intern Med* 1977; **87**: 649–55.
12. Horsman A, Gallagher JC, Simpson M, Nordin BEC. Prospective trial of oestrogens and calcium in postmenopausal women. *Br Med J* 1977; **ii**: 789–92.
13. Kanis JA, Passmore R. Calcium supplemenation of the diet: not justified by present evidence. *Br Med J* 1989; **298**: 137–40, 205–8.
14. Stevenson JC. Calcium supplementation of the diet. *Br Med J* 1989; **298**: 1034.
15. Kanis JA, Passmore R. Calcium supplementation of the diet. *Br Med J* 1990; **300**: 1523.
16. Nordin BEC, Heaney RP. Calcium supplementation of the diet: justified by present evidence. *Br Med J* 1990; **300**: 1056–60.
17. Holbrook TL, Barrett-Connor E, Wingard DL. Dietary calcium and risk of hip fracture: 14 year prospective population study. *Lancet* 1988; **ii**: 1046–9.
18. Stevenson JC, Whitehead MI. Non-hormonal treatment of osteoporosis. *Br Med J* 1982; **285**: 585–8. *Br Med J* 1983; **286**: 1647.
19. Christiansen C, Christiansen MS, McNair P, Hagen C, Stocklund K, Transbol I. Prevention of early post-menopausal bone loss. Controlled 2 year study in 315 normal females. *Eur J Clin Invest* 1980; **10**: 273–9.
20. Nilas L, Christiansen C, Rodbro P. Oral calcium without effect on postmenopausal bone loss. In: Christiansen C, Arnaud D, Nordin BEC, Parfitt AM, Peck WA, Riggs BL, eds. *Osteoporosis: Proceedings of the Copenhagen International Symposium on Osteoporosis* 1984; **2**: 639–42.
21. Nilas L, Christiansen C, Rodbro P. Calcium supplementation and post-menopausal bone loss. *Br Med J* 1984; **289**: 1103–6.
22. Melik RA. The treatment of osteoporosis. *Med J Aust* 1986; **144**: 645–7.
23. Harrison M, Fraser R, Mullan B. Calcium metabolism in osteoporosis. Acute and long-term response to increased calcium intake. *Lancet* 1961; **i**: 1015–19.
24. Cohn SH, Dombrowski CS, Hauser W, Atkins HL. High calcium diet and the parameters of calcium metabolism in osteoporosis. *Am J Clin Nutr* 1968; **21**: 1246–53.
25. Nordin BEC, Peacock M, Aaron J *et al.* Osteoporosis and osteomalacia. *Clin Endocrinol Metab* 1980; **9**: 177–205.
26. Tovey FI, Karamanolis DG, Godfrey J, Clark CG. Postgastrectomy nutrition: methods of out-patient screening for osteomalacia. *Human Nutrition: Clinical Nutrition* 1985; **39c**: 439–46.
27. Pye DW, Hanna WJ, Hesp R. Effective dose equivalent in dual energy X-ray absorptiometry. *Br J Radiol* 1990; **63**: 149 (Letter).
28. Nilsen KH, Jayson MIU, Dixon AStJ. Microcrystalline calcium hydroxyapatite in corticosteroid-treated patients: a controlled study. *Br Med J* 1987; **ii**: 1124–6.
29. Pines A, Raafat H, Lynn AH, Whittington J. Clinical trial of microcrystalline hydroxyapatite compound (Ossopan) in the prevention of osteoporosis due to corticosteroid therapy. *Curr Med Res Opin* 1984; **8**: 734–42.
30. Stellon A, Davies A, Webb A, Williams R. Microcrystalline hydroxyapatite compound in prevention of bone loss in corticosteroid treated patients with chronic active hepatitis. *Postgrad Med J* 1985; **61**: 791–6.
31. Brenton DP, Dent CE. Idiopathic juvenile osteoporosis. In: Bukel H, Sten J, eds. *Inborn Errors of Calcium Metabolism.* Lancaster: MTP Press, 1976: 222–38.
32. Dent CE, Davies IJT. Calcium metabolism in bone disease: effects of treatment with microcrystalline calcium hydroxyapatite compound and dihydrotachysterol. *J R Soc Med* 1980; **73**: 780–5.
33. Galasko CSR, Russell S, Rushton S. Microcrystalline hydroxyapatite in patients with Colles' fractures. In: Christiansen C, Arnaud CB, Nordin BEC, Parfitt AM, Peck WA, Riggs BL, eds. *Osteoporosis: Proceedings of the Copenhagen International Symposium on Osteoporosis* 1984; **2**: 663–4.
34. Epstein O, Kato Y, Dick R, Sherlock S. Vitamin D, hydroxyapatite and calcium gluconate in treatment of cortical bone thinning in post-menopausal women with primary biliary cirrhosis. *Am J Clin Nutr* 1982; **36**: 426–30.
35. Annefield M, Caviezel R, Schaat E, Schicketanz KH. The influence of ossein-hydroxyapatite compound (Ossopan) on the healing of a bone defect. *Curr Med Res Opin* 1986; **10**: 241–50.
36. Reddi AH, Anderson WA. Collagenous bone matrix-induced endochondrial ossification and haemoporesis. *J Cell Biol* 1976; **69**: 557–72.
37. Urist MR, de Lange RJ, Fineman GAM. Bone cell differentiation and growth factor. *Science* 1983; **222**: 680–6.
38. Drivdahl RH, Howard GA, Baylink DJ. Extracts of bone contain a potent regulator of bone formation. *Biochim Biophys Acta* 1982; **714**: 26–33.
39. Exton-Smith AN, Millare PH, Payne PR, Wheeler EF. Pattern of development and bone loss with age. *Lancet* 1969; **ii**: 1154–7.
40. Tovey FI, Godfrey JE, Clark CG. Postgastrectomy nutritional deficiencies: the need for vigilance increases with age. *Geriatr Med Today* 1986; **5**: 68–77.

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Treatment of severe postvagotomy/postgastrectomy symptoms with the somatostatin analogue octreotide

Fourteen patients with severe and persistent postvagotomy/postgastrectomy symptoms were entered into a trial of treatment with the somatostatin analogue octreotide, 50 µg twice daily 30 min before meals being self-administered by subcutaneous injection. Six of the seven patients completing the 3-month trial showed sustained overall improvement of symptoms. The remaining patients were unhelped by treatment or developed unwanted effects. Six of eight patients with dumping syndrome showed sustained improvement of dumping symptoms during treatment. Bile vomiting was relieved in three of four patients with this complaint. Diarrhoea accompanying dumping showed a variable response to treatment, with improvement in three patients and no change or worsening of this symptom in five. Two patients with severe postvagotomy diarrhoea alone showed no improvement. Four patients with unwanted effects and three patients who found no benefit stopped the trial medication early. Four further patients reported mild or transient side-effects. For patients with severe postvagotomy/postgastrectomy symptoms, a trial of octreotide seems justified when significant dumping symptoms are present and other treatment options have been exhausted.

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Vagotomy or gastric resection may result in persistent gastrointestinal symptoms, including the dumping syndrome (synonyms: dumping, early dumping, vasomotor dumping), bile vomiting, diarrhoea and reactive hypoglycaemia (synonym: late dumping). Other symptoms include postcibal nausea, postcibal colic and bloating. Several mechanisms have been suggested as being contributory to these symptoms, including rapid gastric emptying[1], disorganized duodenojejunal motility[2], rapid small bowel transit[3], osmotic transfer of body water to the gut lumen[1], and abnormal release of gut hormones[4] and vasoactive peptides[5].

Mild or infrequent symptoms may require no more than an explanation and reassurance and dietetic advice is sometimes helpful. Conventional drug treatments do not provide sustained relief from severe symptoms and remedial operations may be successful, but are often disappointing. Several studies have shown that the symptoms of dumping in response to a test meal are ameliorated by somatostatin and its long-acting analogue octreotide. The typical accompanying tachycardia and haemoconcentration, or the 'dumping score', are also improved[6–9]. Furthermore, case reports suggest that octreotide is effective in the treatment of reactive hypoglycaemia[10]. The effect of octreotide on postvagotomy diarrhoea is much less clear-cut and reports have been conflicting[8,11]. While octreotide may be helpful in some cases of secretory diarrhoea[12,13] and is reported to have been effective in the short bowel syndrome[14,15], diarrhoea owing to fat malabsorption might be aggravated[15] or may even be a side-effect[16].

The mechanisms by which octreotide ameliorates postvagotomy/postgastrectomy symptoms are unclear but may include a reduction in the rate of gastric emptying[17], modification of midgut motility and transit times[15,18,19], reduction of gut secretion and absorption[20,21], and inhibition of the release of gut hormones and peptides[22].

A recent trial of octreotide in patients with dumping syndrome indicated some benefit from long-term treatment but clinical details were inadequate[23].

To date there has been no clinical study of octreotide in the treatment of patients with a wide variety of postvagotomy/postgastrectomy symptoms which has included more than two patients treated for more than 2 weeks. The present study was designed to evaluate the clinical response to octreotide given for 3 months in patients with a variety of postvagotomy/postgastrectomy symptoms.

Patients and methods

Thirty-six patients with persistent troublesome postvagotomy/postgastrectomy symptoms presented over a 3-year period from June 1987. Initial management consisted of explaining to patients the nature of their symptoms and the treatment options available. Patients underwent full investigation, including gastroscopy and upper abdominal ultrasonography in all cases, barium enema and/or colonoscopy in patients with diarrhoea, and jejunal biopsy and [^{14}C]glycocholate breath testing in patients with diarrhoea alone, to exclude other diagnoses before inclusion in the study was considered.

Following assessment and counselling, 14 patients with severe symptoms opted for a trial of treatment with octreotide on the understanding that even if the treatment proved successful it would still be stopped after 3 months to allow a further period to assess symptoms. All patients entered into the trial were admitted to hospital for pre-treatment investigations to observe, define and score their symptoms. These investigations included a dumping provocation test in all cases and faecal fat excretion studies in patients with diarrhoea as the major symptom. Where possible, patients underwent gastric emptying studies before admission. For dumping provocation tests, fasted patients drank 150 ml 50 per cent dextrose; pulse rate, haematocrit and blood sugar levels were measured twice before, and at intervals for 3 h after, the test drink. Symptoms provoked by the test drink were observed and recorded. Gastric emptying of 15 per cent dextrose (300 ml) was assessed as previously described[24] and was expressed as the percentage of test meal emptied from the stomach 4 min after the 6-min ingestion period.

A positive response to the dumping provocation tests consisted of observed unequivocal symptoms and/or pathognomonic changes in pulse rate and haematocrit in response to the test meal, calculated as a 'dumping score'[25]. A convincing history and a positive test were

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required to substantiate the diagnosis. Diarrhoea as a feature of dumping syndrome was accepted on the basis of a positive dumping provocation test with two or more watery or urgent bowel movements during the test or noted daily in patients' symptom diaries. Postvagotomy diarrhoea in the absence of dumping was accepted only when four or more watery or urgent bowel movements occurred in response to the dumping provocation test. A diagnosis of bile vomiting or postcibal colic was accepted on the basis of history alone. A diagnosis of reactive hypoglycaemia was based on the finding of a subnormal ($<2\cdot0$ mM) blood glucose level following the dumping provocation test meal.

The severity of symptoms before and during treatment was scored on a six-point scale, each point corresponding to a detailed predetermined statement concerning an individual's ability to work and enjoy normal social activities (*Table 1*). For the first six patients studied, symptom scores before and during treatment were determined on the basis of detailed questionnaires, symptom diaries completed daily by patients, and on interviews. For the remainder of the trial the severity of symptoms was scored on to proformas using the same system by a single consultant gastroenterologist not involved in the trial in any other way. Scores were assigned to each major symptom, and the single worst score taken to represent the overall score. Symptom scoring was carried out before the start of treatment, after 3–5 weeks, and again after 3 months of treatment or at the cessation of treatment for patients who withdrew before the end of the trial. The same system was also applied to new unwanted effects of treatment.

The clinical details of the 14 patients entered into the trial are summarized in *Table 2*. Eleven patients had their first operations carried out for the treatment of chronic or complicated peptic ulcer disease and three for severe gastric mucosal dysplasia, adenocarcinoma of the stomach, or oesophageal squamous carcinoma *in situ*. Eight of the 14 patients had previously undergone between one and three further operations intended to relieve their postoperative symptoms.

Table 1 *Description of the scoring system*

	Symptoms	
Score	Summary	Details
0	None	No symptoms, or symptoms so minor that no action has been required and they have had no effect on ability to work, on social and recreational activity and enjoyment of life.
1	Present but not a problem	Minor symptoms requiring minor adjustments to social, recreational and/or work routine but not affecting work performance or enjoyment of life.
2	Minor, manageable	Symptoms which have necessitated changes in work routine and/or social activities such that maximum work performance and/or fullest enjoyment of life is not attainable. Work performance is nevertheless satisfactory, and social and recreational activities enjoyable to an acceptable degree.
3	Moderate; a problem but can cope	Because of symptoms, difficulty is being experienced in maintaining satisfactory work performance (or would be, if seeking employment). Unable to participate in social and recreational activities to an extent that affects enjoyment of life. Nevertheless, still active to an enjoyable extent.
4	Severe; impairs lifestyle	Because of symptoms, change to a less demanding, downgraded or part-time job required (or would need to, if seeking employment). Ability to participate in social and recreational activities limited, such that enjoyment of life is severely compromised.
5	Debilitating, crippling	As a direct result of symptoms, unable to work and/or unable to participate in social and recreational activities, such that enjoyment of life is as badly compromised as it could be.

Following pre-treatment investigation and assessment, patients entered into the trial were started on octreotide (Sandostatin®, Sandoz Pharmaceuticals, Frimley, Surrey, UK) 50 µg subcutaneously twice daily 30 min before the two main meals of the day, usually at about 12.00 and 18.00 hours. Patients were taught to give their own injections and were then discharged.

All patients in the trial were reviewed in clinic every 3 weeks until at least 6 weeks after cessation of treatment. When possible, gastric emptying studies and dumping provocation tests were repeated during the trial period, at least 2 weeks after starting treatment, with octreotide administration 30 min before test meal administration for these studies.

In order that the effects of treatment could be studied in isolation, all other medications used by the patient to treat their gastrointestinal symptoms were stopped before the trial, and any unwanted effects of treatment developing during the trial were not treated with other drugs. All patients gave written informed consent. The study was approved by the local ethical committee.

Results

Overall response to treatment

Six of the 14 patients entered into the trial completed 12 weeks of continuous treatment. A seventh patient (patient number 12) who ran out of her supply of octreotide after 60 days but who would otherwise have continued with treatment was, for the purpose of this analysis, deemed to have completed the trial. Six of these seven patients showed an overall improvement in their symptoms during the trial and five have since requested further courses of treatment. The sixth patient (patient number 6) underwent revisional surgery. One patient who completed the trial but who did not on completion report any overall benefit (patient number 8) had shown interim improvements of dumping and bile vomiting.

Among the remaining seven patients in the trial, one patient (patient number 2) had his treatment stopped by us at 34 days after reporting possible side-effects of treatment, despite complete remission of his dumping and bile vomiting. The other six patients all withdrew before completing the trial because their symptoms were unchanged (patient numbers 1 and 5), worsened by the treatment (patient numbers 7 and 13), or because they were unable to tolerate the injections (patient numbers 11 and 14).

Dumping

Nine patients had abnormally high scores in their pre-treatment dumping provocation tests (*Figure 1*), eight with clinically evident dumping symptoms, the ninth having profuse diarrhoea only (patient number 5). Of the remaining five patients, three had normal scores and developed neither dumping symptoms nor diarrhoea during the test. One patient (patient number 7) developed profuse diarrhoea in response to the test which was unscored because of a blood sample error. The remaining patient (patient number 4) appeared to exhibit dumping symptoms during the test but had a normal test score. All patients with abnormally high dumping provocation test scores had normal or lower scores and an absent or reduced symptomatic response when re-tested on treatment (*Figure 1*).

One patient with pre-treatment symptoms of dumping (patient number 14) insisted that the treatment was of no benefit, despite the obvious amelioration of symptoms witnessed during repeat dumping provocation testing. Another patient (patient number 8) reported an improvement in his dumping symptoms halfway through the trial, corresponding to a negative dumping provocation test at this time, but felt that this benefit had been lost by the end of the trial and declined a final test. A third patient (patient number 9) was judged independently not to have dumping symptoms yet had a positive dumping provocation test (symptoms and score) and showed marked improvement, both symptomatically and to testing, throughout the course of the trial. The remaining six patients with high pre-trial dumping scores showed abolition

Table 2 *Clinical details of patients included in the trial*

Patient no.	Sex	Age (years)	Duration of symptoms (years)	Original operation	Revisional operations	Duration of trial (days)	Symptoms	Symptom score: Before treatment	Symptom score: During trial	Symptom score: At end of trial	Sustained overall symptomatic improvement
1	M	64	37	Pólya partial gastrectomy	Stoma revision Adhesiolysis	28	Postcibal colic	4	4		No
2	M	38	9	Truncal vagotomy with pyloroplasty	Gastrojejunostomy	34	Dumping‡ Diarrhoea (C) Bile vomiting	5 4 2	0 4 0		No
3	M	33	2	Partial gastrectomy, Roux-en-Y gastrojejunostomy		84*†	Dumping‡ Diarrhoea (E)	4 2	0 2	0 3	Yes
4	F	48	2	Highly selective vagotomy with fundoplication		104*†	?Dumping‡ Diarrhoea (C)	4 1	4 1	2 2	Yes
5	M	34	5	Truncal vagotomy with pyloroplasty	Pyloric reconstruction Repeat pyloric reconstruction	34	Diarrhoea‡ (C)	5	5		No
6	M	59	1	Truncal vagotomy with pyloroplasty		102*	Dumping‡ Diarrhoea‡ (C)	4 4	1 1	1 3	Yes
7	M	64	5	Truncal vagotomy with pyloroplasty	Re-vagotomy, partial gastrectomy, Roux-en-Y gastrojejunostomy Distal reversed ileal segment	5	Diarrhoea‡ (C)	4	5		No
8	M	45	12	Truncal vagotomy with pyloroplasty	Billroth I partial gastrectomy Gastrojejunostomy	89*	Dumping‡ Diarrhoea (C) Hypoglycaemia Postcibal colic Bile vomiting	5 4 4 3 3	3 4 2 3 1	5 4 4 3 1	No
9	M	56	1/2	Total gastrectomy	Revision of oesophagojejunostomy with jejunal pouch	107*†	Postcibal nausea‡ Postcibal colic Diarrhoea (E)	5 4 2	2 1 3	0 1 1	Yes
10	M	52	12	Truncal vagotomy with pyloroplasty	Antrectomy, Roux-en-Y gastrojejunostomy	90*†	Diarrhoea‡ (E) Dumping Postcibal colic	5 4 3	4 2 2	2 2 3	Yes
11	F	70	4	Oesophagogastrectomy (Ivor-Lewis)		2	Postcibal nausea‡ Bile vomiting	4 3			No
12	F	64	19	Pólya partial gastrectomy		60*†	Dumping‡ Hypoglycaemia Postcibal colic Bile vomiting Diarrhoea (E)	5 4 3 2 2	2 2 1 0 2		Yes
13	M	50	22	Truncal vagotomy with pyloroplasty	Partial gastrectomy, Roux-en-Y gastrojejunostomy	6	Postcibal nausea‡ Postcibal bloating Dumping	4 3 2	4 5 0		No
14	F	52	2	Truncal vagotomy with antrectomy		7	Dumping‡ Postcibal colic Diarrhoea (C)	4 3 3	? ? ?		No

* Trial completed; † further courses of treatment requested by patient; ‡ most severe symptom before treatment; C, continuous; E, episodic

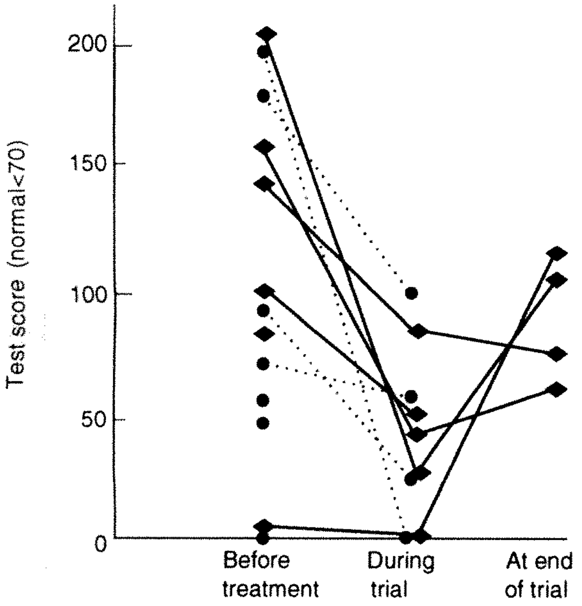

Figure 1 *Dumping provocation test scores based on pulse rate and haematocrit changes at 15 min*[25]. *Patients showing sustained overall improvement in symptoms during trial* (—◆—) *and those showing no overall symptomatic improvement during trial* (· · · ● · · ·)

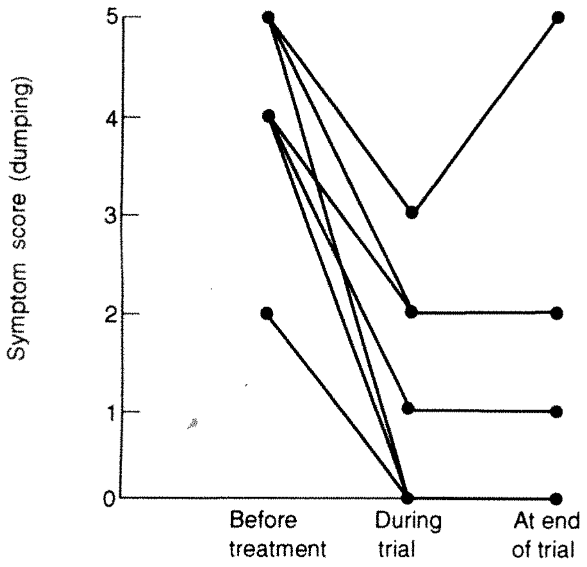

Figure 2 *Symptom scores for patients with dumping* (*see also* Table 2)

or sustained improvement of their dumping symptoms throughout the treatment period (*Figure 2*).

Diarrhoea

Neither patient with postvagotomy diarrhoea alone (patient numbers 5 and 7) was helped at all by treatment with octreotide. In patients with dumping and diarrhoea the effect of treatment upon their diarrhoea was variable: three patients showed some improvement, three continued unchanged, and in two patients this symptom became more troublesome. A ninth patient (patient number 14) had symptoms that were not reliably evaluable. One patient with dumping but no diarrhoea (patient number 13) developed urgent early morning diarrhoea during his 1-week trial of treatment. The remaining two patients in the trial entered with symptoms other than dumping and diarrhoea. One of these patients developed loose stools during the trial (patient number 1). The other patient had no disturbance of bowel habit in response to treatment which lasted for only 2 days (patient number 11).

Other symptoms

Among four patients with significant bile vomiting, three were relieved of this symptom during treatment with octreotide. The fourth patient in this group (patient number 11) did not continue with treatment long enough to have the response evaluated. Postcibal colic was ameliorated by treatment in three patients, was unchanged in two, and was not evaluable in the sixth patient. Reactive hypoglycaemia was ameliorated in the two patients with this symptom, although this improvement may have been temporary for patient number 8.

Postcibal nausea was relieved by octreotide in one patient (patient number 9); the other patient with this symptom (patient number 11) discontinued treatment before the response could be evaluated. In one patient (patient number 13) a complaint of postcibal bloating was aggravated by treatment, leading to this patient's withdrawal from the trial after 1 week.

Other measured effects

Nine of 11 patients exhibited rapid gastric emptying of the liquid test meal before treatment. No consistent change in gastric emptying could be identified during the trial of treatment (*Figure 3*).

Two patients (patient numbers 1 and 5) showed marked increases in faecal fat excretion during the course of the trial (*Figure 4*). An insufficient number of patients was able to complete these studies for definitive conclusions to be drawn.

There was no consistent change in patients' body-weights during the course of treatment with octreotide; weight changes during treatment varied between a gain of 5 kg (patient number 9) and a loss of 5 kg (patient number 12).

Side-effects

Two of three patients not previously complaining of diarrhoea developed diarrhoea during treatment, and three further patients had their complaint of diarrhoea aggravated during

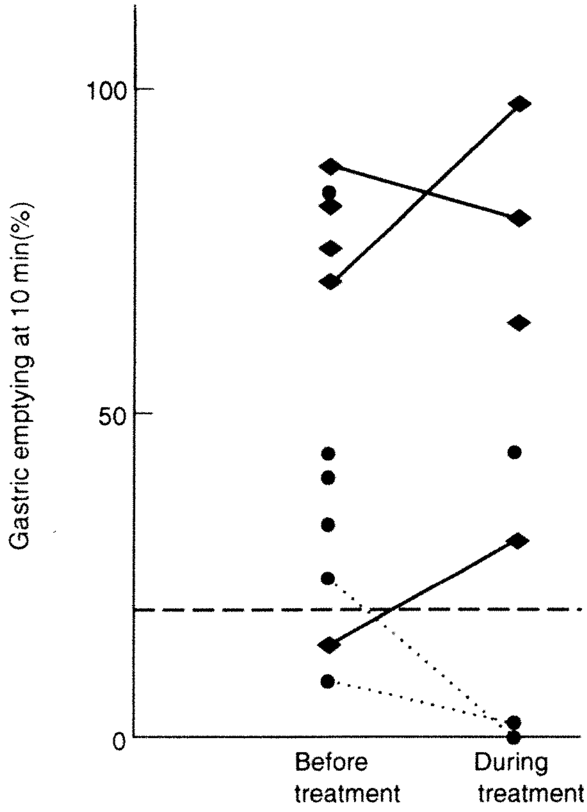

Figure 3 *Results of gastric emptying studies. Patients showing sustained overall improvement in symptoms during trial* (—◆—), *those showing no overall symptomatic improvement during trial* (· · · ● · · ·) *and upper limit of normal* (– – –)

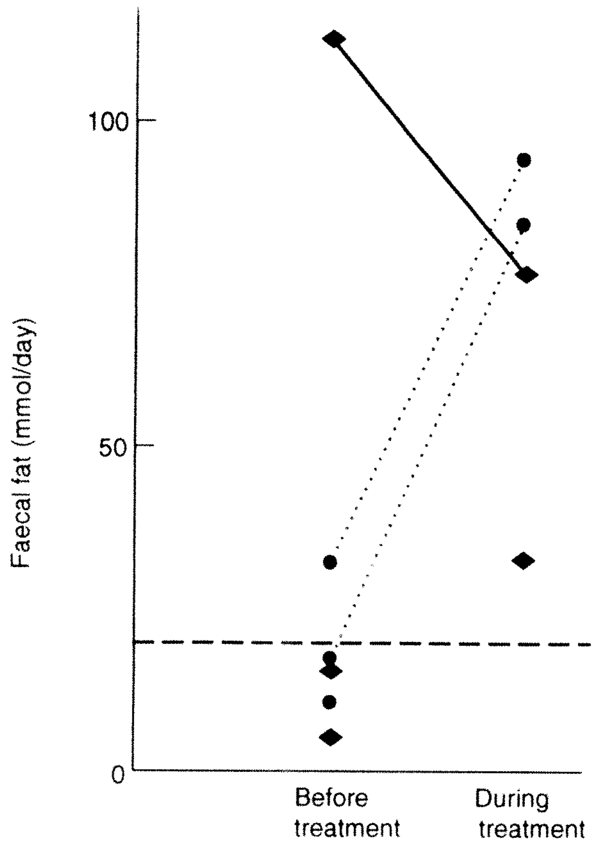

Figure 4 *Results of faecal fat studies. Patients showing sustained overall improvements in symptoms during trial (—◆—), those showing no overall symptomatic improvement during trial (···●···) and upper limit of normal (– – –)*

the trial. In these patients and in those whose diarrhoea was unchanged in severity during the trial, there was a noticeable tendency for their diarrhoea to develop – or change to – a distinct daily periodicity, occurring with some urgency in the early morning and being less troublesome or absent during the rest of the day.

Two patients (patient numbers 11 and 14) withdrew from the trial after 2 and 7 days respectively because they were unable to tolerate the injections. They experienced symptoms similar to those reported by six other patients immediately following injections and lasting for a few minutes: headache, paraesthesia, dizziness, cramps, faintness, flushing and 'panic attacks'.

Two patients complained of tiredness as a result of disturbed bowel habit in the early mornings. Two patients complained of loss of appetite, remitting in the patient who continued on treatment. One patient (patient number 2) reported the development of dizziness, light-headedness and photophobia during the first 5 weeks of treatment and was noted to have developed a mild elevation of serum γ-glutamyl transferase. His trial of treatment was therefore stopped at day 34.

No other side-effects or changes in routine blood parameters occurred during or after trial courses of treatment. One patient (patient number 3) reported continuing relief of dumping symptoms after cessation of treatment with a gradual return of pre-treatment symptoms over several weeks. All other patients reported an abrupt return to pre-treatment symptom status within 1–2 days of stopping treatment. No instance of rebound exaggeration of symptoms was identified.

Discussion

In a study such as this a patient's subjective response to a new treatment may be influenced by the attention focused upon him/her during the consultative process. On occasion, patients may indeed remit on seeing that their symptoms are believed. It should be remembered that octreotide may have analgesic properties and possibly modifies a patient's mood or influences their perception of symptom severity as a result[26].

Patients who have symptoms because of disturbed gut physiology after gastric surgery cannot readily be brought together as a clinically homogeneous group. We felt it would be useful to include patients with symptoms other than dumping syndrome because neither the pathophysiological relationship between various symptoms nor the manner in which octreotide might usefully modify them is clearly understood.

During the course of this study we modified the protocol to introduce independent assessment of patients' symptoms both before and during the trial, hoping thereby to make these assessments more objective. We did not, however, notice any discrepancies between severity scores assigned by the consultant gastroenterologist and those we would ourselves have given. The discrepancies that did occur concerned the nature of symptoms rather than their severity.

Some further information about the individuals studied may help to explain some of the results. Patient number 2, who was withdrawn from the study, was understood to have substantially increased his alcohol intake during the trial. It may be that the side-effects reported and the observed elevation of serum γ-glutamyl transferase were related to this rather than to his treatment. Patient number 4 had a clinical diagnosis of dumping syndrome made by several specialists. Her dumping provocation test was positive on the basis of symptoms witnessed during testing, but there was no other objective evidence of the diagnosis, and it may be that she had a quite different disorder of vasomotor episodes which were, nevertheless, responsive to treatment with octreotide.

Although the response to treatment was extremely variable, dumping symptoms were consistently ameliorated. For most patients in this group, the effect was immediate and dramatic. Generally, this specific benefit persisted throughout the trial of treatment, but was offset by the continuation and in some cases worsening of other symptoms or the development of other unwanted effects. The clinical response of dumping symptoms to treatment was associated with an improved response to dumping provocation tests carried out during the treatment period. The results of gastric emptying studies do not support the suggestion that improvement of dumping symptoms is due, even in part, to reduction of abnormally rapid gastric emptying.

Neither of the patients with postvagotomy diarrhoea alone were helped by treatment. Both of these patients subsequently underwent distal ileal reversed onlay patch operations[27], again without benefit. These results, and the variable effect of treatment upon diarrhoea in patients with dumping, suggest that there may be more than one pathophysiological explanation for postvagotomy diarrhoea. Conversely, the coexistence of dumping and bile vomiting, with the relief of both symptoms by octreotide might suggest that these symptoms reflect different aspects of the same physiological disturbance.

Octreotide proved to be efficacious in the control of dumping symptoms to a degree previously unmatched by other pharmacological means. However, the lack of specificity of this treatment, resulting in unwanted effects, combined with the difficulties of the treatment regimen itself, makes it unsuitable for long-term use in many cases. We recruited 'problem patients' with severe symptoms unresponsive to conventional dietetic and medical management who were unsuitable or unwilling to undergo further revisional surgery. Clinicians dealing with such patients might reasonably consider offering a trial of treatment with octreotide when symptoms include dumping or bile vomiting and the response to dumping provocation testing has been abnormal. We would caution that any such patient should be kept under close review since unwanted effects in them seem common and the drug is still under intensive surveillance.

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References

1. Ralphs DNL, Thomson JPS, Haynes S, Lawson-Smith C, Hobsley M, LeQuesne LP. The relationship between the rate of gastric emptying and the dumping syndrome. *Br J Surg* 1978; **65**: 637–41.
2. Pandolfo N, Nebiacolombo C, Bortolotti M, Mattioli F. Pyloric reflux: a duodenal functional problem? *Scand J Gastroenterol* 1979, **14**(Suppl 54): 62–6.
3. Thompson DG, Ritchie HD, Wingate DL. Patterns of small intestinal motility in duodenal ulcer patients before and after vagotomy. *Gut* 1982; **23**: 517–23.
4. Lawaetz O, Blackburn AM, Bloom SR, Aritas Y, Ralphs DNL. Gut hormone profile and gastric emptying in dumping syndrome: a hypothesis concerning the pathogenesis. *Scand J Gastroenterol* 1983; **18**: 73–80.
5. Cuschieri A, Worthington K. Kinin levels in the peripheral venous blood of patients with severe vasomotor dumping before and after revisional surgery. *Br J Surg* 1976; **63**: 210–12.
6. Long RG, Adrian TE, Bloom SR. Somatostatin and the dumping syndrome. *Br Med J* 1985; **290**: 886–8.
7. Hopman WPM, Wolberink RGJ, Lamers CBHW, van Tongeren JHM. Treatment of the dumping syndrome with the somatostatin analogue SMS 201-995. *Ann Surg* 1988; **207**: 155–9.
8. Primrose JN, Johnston D. Somatostatin analogue SMS 201-995 (octreotide) as a possible solution to the dumping syndrome after gastrectomy or vagotomy. *Br J Surg* 1989; **76**: 140–4.
9. Tulassay Z, Tulassay T, Gupta R, Cierny G. Letter. *Ann Surg* 1989; **210**: 250–2.
10. D'Cruz DP, Reynard J, Tatman AJ, Kopelman PG. Long-term symptomatic relief of postprandial hypoglycaemia following gastric surgery with a somatostatin analogue. *Postgrad Med J* 1989; **65**: 116–17.
11. Santangelo WC, Dueno MI, Pike I, Estes BL, Krejs GJ. Clinical efficacy of the somatostatin analog 201-995 in the post-gastrectomy dumping syndrome. *Gastroenterology* 1987; **92**: 1613(Abstract).
12. Fuessl HS, Zoller WG, Kochen MM *et al*. Treatment of secretory diarrhoea in AIDS with the somatostatin analogue SMS 201-995. *Klin Wochenschr* 1989; **67**: 452–5.
13. Edwards CA, Cann PA, Read NW, Holdsworth CD. The effect of somatostatin analogue SMS 201-995 on fluid and electrolyte transport in a patient with secretory diarrhoea. *Scand J Gastroenterol* 1986; **2**(Suppl 119): 259–61.
14. Ladefoged K, Christensen KC, Hegnhoj J, Jarnum S. Effect of a long acting somatostatin analogue SMS 201-995 on jejunostomy effluents in patients with severe short bowel syndrome. *Gut* 1989; **30**: 943–9.
15. Cooper JC, Williams NS, King RFGJ, Barker MCJ. Effects of a long-acting somatostatin analogue in patients with severe ileostomy diarrhoea. *Br J Surg* 1986; **73**: 128–31.
16. Wass JAH, Lytras N, Besser GM. Somatostatin octapeptide (SMS 201-995) in the medical treatment of acromegaly. *Scand J Gastroenterol* 1986; **21**(Suppl 119): 136–40.
17. Parr NJ, Jenkins S, Grime S, Critchley M, Baxter JN, Mackie CR. Somatostatin analogue (SMS 201-995) inhibits rapid gastric emptying of liquid following truncal vagotomy with drainage. *Surg Res Comm* 1988; **2**: 193–7.
18. Dueno MI, Bai JC, Santangelo WC, Krejs GJ. Effect of somatostatin analog on water and electrolyte transport and transit time in human small bowel. *Dig Dis Sci* 1987; **32**: 1092–6.
19. Neri M, Cuccurullo F, Marzio L. Effect of somatostatin on gallbladder volume and small intestinal motor activity in humans. *Gastroenterology* 1990; **98**: 316–21.
20. Lucey MR. Endogenous somatostatin and the gut. *Gut* 1986; **27**: 457–67.
21. O'Donnell LJD, Farthing MJG. Therapeutic potential of a long acting somatostatin analogue in gastrointestinal diseases. *Gut* 1989; **30**: 1165–72.
22. Williams G, Fuessl H, Kraenzlin M, Bloom SR. Postprandial effects of SMS 201-995 on gut hormones and glucose tolerance. *Scand J Gastroenterol* 1986; **21**(Suppl 119): 73–83.
23. Geer RJ, Richards WO, O'Dorisio TM *et al*. Efficacy of octreotide acetate in treatment of severe postgastrectomy dumping syndrome. *Ann Surg* 1990; **212**: 678–87.
24. Parr NJ, Grime S, Brownless S, Critchley M, Baxter JN, Mackie CR: Relationship between gastric emptying of liquid and postvagotomy diarrhoea. *Br J Surg* 1988; **75**: 279–82.
25. Linehan IP, Weiman J, Hobsley M. The 15-minute dumping provocation test. *Br J Surg* 1986; **73**: 810–12.
26. Paunovic VR, Popovic V. The development of dependence to an octapeptide somatostatin analog: contribution to the study of somatostatin analgesia. *Biol Psychiatry* 1989; **26**: 97–101.
27. Cuschieri A. Surgical management of severe, intractable postvagotomy diarrhoea. *Br J Surg* 1986; **73**: 981–4.

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Comparison of minimal and conventional surgery in patients with bleeding peptic ulcer: a multicentre trial

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A multicentre randomized prospective trial compared minimal surgery (under-running the vessel or ulcer excision and adjuvant ranitidine) with conventional ulcer surgery (vagotomy and pyloroplasty or partial gastrectomy) for the treatment of bleeding peptic ulcer. This report is based on 137 patients (eight withdrawn through misdiagnosis or lost data), of whom 62 received conservative surgery and 67 conventional operation. Twenty-nine patients died, 16 (26 per cent) after conservative surgery and 13 (19 per cent) after conventional operations. The only significant difference between the groups was the incidence of fatal rebleeding, which occurred in six patients after conservative surgery compared with none after conventional surgery ($P < 0{\cdot}02$*, Fisher's exact test).*

The mortality rate from peptic ulcer haemorrhage is extremely variable[1] but has remained at approximately 10 per cent despite advances in endoscopic therapy and the pharmacological control of acid secretion. The operative mortality rate is also variable, ranging from 8 to 33 per cent[2,3]. Recently, a conservative approach to bleeding peptic ulcer has been adopted by under-running the bleeding vessel through a pylorotomy (closed as a pyloroplasty) combined with truncal vagotomy in preference to partial gastrectomy. Many perform more conservative surgery by under-running the vessel through a duodenotomy or gastrotomy to achieve haemostasis, combined with H_2-antagonist therapy[4].

Rebleeding is the single most important factor in determining the mortality rate[5], and in severely compromised patients, particularly the elderly, the choice of surgery is contentious. The majority of patients with bleeding peptic ulcer are elderly, many having coexisting cardiovascular, respiratory or renal disease, and at least half are taking non-steroidal anti-inflammatory drugs. These factors probably contribute to the high postoperative mortality rate and may predispose towards rebleeding.

The aim of surgical intervention is to arrest haemorrhage, some surgeons maintaining that under-running alone, with H_2-antagonists, is a safer option than gastrectomy or oesophageal mobilization and vagotomy[6]. Others argue that conventional operations reduce the risks of rebleeding and recurrent ulcer[7].

These different approaches to the surgical management of peptic ulcer haemorrhage were compared in a randomized prospective trial.

Patients and methods

The criteria for surgical intervention were based on the results of a previous trial[8], patients being stratified according to age (18–60 or 61–90 years) and managed according to a defined surgical protocol; patients of all ages underwent surgical treatment if at endoscopy there was a spurting vessel causing exsanguinating haemorrhage.

The criteria for operation on patients aged between 18 and 60 years were the need for 8 or more units of blood or colloid for replacement of blood volume, or two rebleeds in hospital. For those aged 61–90 years, the criteria for operation were 4 or more units of blood or colloid for replacement of blood volume or one rebleed in hospital.

As soon as the criteria for surgery were fulfilled and the decision to operate made, patients were randomized to receive conservative or conventional surgery. Separate sets of randomization envelopes were used for patients with gastric and duodenal ulcers (GU and DU).

Conservative surgery involved under-running the vessel through a gastrotomy or duodenotomy using at least four deep encircling sutures or ulcer excision. Adjuvant intravenous ranitidine 50 mg 8-hourly was given until oral full-dose ranitidine (150 mg twice a day) could be tolerated, which was continued for at least 6 weeks after operation.

Conventional surgery was left to the discretion of the surgeon, but involved either under-running the ulcer through a pylorotomy with truncal vagotomy and subsequent pyloroplasty or a partial gastrectomy. The use of prophylactic subcutaneous heparin and cephalosporin antibiotic was left to the discretion of the surgeon.

In patients in whom it was not possible to perform the randomized operations for anatomical reasons, e.g. deformed pylorus, duodenal stenosis, prepyloric ulcer or giant gastric ulcer, the surgeon performed whatever surgery was feasible. Patients in whom the cause of bleeding was other than a peptic ulcer were withdrawn and excluded from the trial. The study compared postoperative mortality rates and complications, particularly early morbidity from rebleeding or recurrent ulcer.

Results

Fourteen hospitals in 12 cities from three countries contributed a total of 137 patients, of whom 111 received randomized operations. Thirteen underwent an alternative surgical option for anatomical reasons and there were five cases of protocol violation due to delayed surgical intervention, but in which the randomized operations were carried out. Five patients were withdrawn because they were bleeding from a source other than a peptic ulcer (one gastric varix, two Dieulafoy syndrome, two pancreatic cancer), and data were unavailable in three.

Analysis of the results was based on treatment received and excluded the five misdiagnosed patients and three in whom data were unavailable. Sixty-two conservative procedures were carried out (33 GU, 29 DU), of which there were 59 undergoing under-running of the vessel and three having ulcer excision (3 GU). There were 67 conventional operations (29 GU, 38 DU), made up of 25 partial gastrectomies (21 GU, 4 DU) and 42 truncal vagotomies (eight GU, 34 DU), of which 35 patients had the vessel oversewn and three patients with GU underwent ulcer excision.

Postoperative complications

The incidence of complications up to 30 days after operation was similar in both groups with the exception of rebleeding

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Table 1 *Postoperative mortality rate*

	Conservative surgery ($n = 62$)	Conventional surgery ($n = 67$)	Statistical significance*
Overall mortality rate (per cent)	26 ($n = 16$)	19 ($n = 13$)	n.s.
Causes			
Ulcer rebleeding	6 (2)	0	$P < 0\cdot02$
Cerebrovascular	2 (1)	2 (1)	n.s.
Cardiovascular	2 (2)	3 (1)	n.s.
Pulmonary embolism	3	1 (1)	n.s.
Sepsis/multiorgan failure	0	3 (1)	n.s.
Respiratory failure/infection	3	4	n.s.

Values in parentheses are late in-hospital deaths, i.e. >30 days after operation. *Fisher's exact test

from the ulcer, which occurred in seven patients after conservative surgery and four after conventional operation.

Mortality from rebleeding ulcers occurred only after conservative surgery (six of seven cases); one patient exsanguinated before surgical intervention, three suffered cardiovascular effects, and two died of complications from further surgery. The overall mortality rate was 22 per cent; deaths occurred in 16 patients after conservative surgery (26 per cent) compared with 13 after conventional surgery (19 per cent) (*Table 1*).

Discussion

Since 1983, a strict management policy for the treatment of peptic ulcer haemorrhage has been implemented at Birmingham General Hospital, using the criteria for surgery outlined in this study. This policy was developed from a trial of the optimum timing of surgical intervention[8]. Adherence to this management policy, which advocates early aggressive surgery in the elderly, is monitored by continuous weekly audit when all patients with gastrointestinal bleeding are discussed. All patients with bleeding peptic ulcer are admitted to a central unit and managed by physicians and surgeons; the programme has produced mortality rates of less than 5 per cent per annum since 1983. Optimum timing of surgery maintains low mortality rates outside the confines of a clinical trial[9].

The present study aimed to determine whether a policy of conservative surgery could reduce the mortality rate without increasing the risk of complications, particularly recurrent ulcer and rebleeding. To recruit sufficient numbers, a multicentre trial was designed without restricting the use of heparin, and allowing surgeons to abandon the randomized operation if for technical reasons the procedure allocated was not feasible.

The results of this study indicate that the highest morbidity was associated with rebleeding, which often required further surgery. Rebleeding occurred in four patients after conventional surgery (all being oversewn with vagotomy and pyloroplasty) and in seven after conservative surgery, of whom six died. There was no correlation between rebleeding and ulcer site or size, duration of symptoms, status of the surgeon or anaesthetist, or age of the patient. Subcutaneous heparin did not predispose to rebleeding.

Early reports of simple under-running for bleeding gastric ulcer showed poor results, but could be explained by the selection of patients, many of whom were severely ill and considered unfit for conventional surgery. A recent retrospective study of surgical management for bleeding gastric ulcer reported the mortality rate from undersewing alone to be no worse than that for conventional surgical treatment[6].

In this trial the high mortality rate associated with rebleeding after conservative surgery is greater than expected and was not confined to one centre. All patients who rebled after conservative surgery had the vessel under-run rather than ulcer excision. It was recommended that at least four deep sutures should be inserted, but these may not be adequate in all cases and ulcer excision may be a safer option, particularly for gastric ulcer. Excision provides an opportunity for histological examination of the ulcer and may detect early gastric cancers.

In view of the high rates of fatal rebleeding after conservative surgery in this interim analysis, a decision to stop entry into the trial has been made.

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References

1. Allan RN, Dykes P. A study of the factors influencing mortality rates in gastrointestinal haemorrhage. *Q J Med* 1976; **45**: 533–50.
2. Vallon AG, Cotton PB, Laurence BH, Miro JRA, Oses JCS. Randomised trial of endoscopic argon laser photocoagulation in bleeding peptic ulcers. *Gut* 1981; **22**: 228–33.
3. Murray WR, LaFeria G, Rogers P, Archibald M. Maintenance ranitidine prophylaxis after haemorrhage from a duodenal ulcer. *Br J Surg* 1987; **74**: 544.
4. Dronefield MW, Atkinson M, Langman MJS. Effect of different operation policies on mortality from bleeding peptic ulcer. *Lancet* 1979; **i**: 1126–8.
5. Clason AE, Macleod DAD, Elton RA. Clinical factors in the prediction of further haemorrhage or mortality in acute upper gastrointestinal haemorrhage. *Br J Surg* 1986; **73**: 985–7.
6. Rogers PN, Murray WR, Shaw R, Brar S. Surgical management of bleeding gastric ulceration. *Br J Surg* 1988; **75**: 16–17.
7. Hunt PS, Hansky J, Korman MG. Mortality in patients with haematemesis and malaena: a prospective study. *Br Med J* 1979; **1**: 1238–40.
8. Morris SL, Hawker PC, Brearley S, Simms M, Dykes PW, Keighley MRB. Optimal timing of operation for bleeding peptic ulcer: a prospective randomised trial. *Br Med J* 1984; **288**: 1277–80.
9. Hunt PS. Surgical management of bleeding chronic peptic ulcer: a ten year prospective study. *Ann Surg* 1984; **199**: 44–50.

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Palliation of malignant dysphagia with laser therapy: predictability of results

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This study reports the results of 189 patients treated by laser therapy for malignant dysphagia. Ninety-one per cent of patients derived benefit from treatment, but the long-term survival rate was poor, with only 12 per cent of patients surviving for 6 months. Survival was not influenced by either tumour length, site or histological type. Patients with adenocarcinomas initially showed improved swallowing after laser treatment compared with those with squamous tumours, but this difference had disappeared by 2 months. The results of laser treatment were not influenced by either tumour length or site.

Malignant dysphagia from carcinoma of the oesophagus and gastric cardia is becoming an increasing problem. At the time of presentation to the surgeon, only half of the patients have operable disease[1]. The remaining patients, however, still require palliation of their symptoms, especially dysphagia.

Good palliation of dysphagia after treatment with the NdYAG laser has been reported, but not all patients benefit[2–4]. In this study we report the results of our first 189 patients in an attempt to identify those patients who will derive most benefit from laser treatment.

Patients and methods

One hundred and eighty-nine consecutive patients with malignant dysphagia were studied; 119 (63 per cent) were men and the mean(s.d.) age was 73(10) years (range 38–100 years). All patients were either unfit for surgery or had inoperable disease. One hundred and eighty (95 per cent) patients presented with primary tumours and nine (5 per cent) with recurrence following previous resection. The histological classification of the tumours was adenocarcinoma in 145 (77 per cent) patients, squamous carcinoma in 39 (21 per cent) and undifferentiated carcinoma in five (3 per cent). Eighty (42 per cent) tumours were situated in the cardia or stomach, 72 (38 per cent) in the lower third of the oesophagus, and 28 (15 per cent) in the upper two-thirds. The remaining nine patients with recurrence had disease either at the anastomosis or in the stomach. Ninety-three (49 per cent) of the tumours were less than 5 cm in length.

All patients had some degree of dysphagia. Dysphagia was graded from 0 to 4 before treatment and every month thereafter for life (0, normal swallowing; 1, some solids stick; 2, soft diet only; 3, fluids only; 4, total dysphagia).

A NdYAG laser (Fibrelase 100, Living Technology, Glasgow, UK) was used with a wavelength of 1064 nm. A dose of between 5000 and 10 000 J was given for each treatment. Initially two treatments were given, separated by 3 days, followed by repeat treatments once a month. If it was not possible to pass the endoscope into the stomach, the oesophagus was dilated with a Celestin dilator passed over a guidewire. Laser treatment was then undertaken, starting at the distal margin of the tumour.

Survival was calculated from the time of referral. In all cases with primary tumours, except three patients with squamous carcinoma who had previously had radiotherapy, this was within 3 weeks of presentation to hospital. No patient received adjuvant radiotherapy.

Results

Of the 189 patients, 19 (10 per cent) are still alive and under review. A total of 633 treatments was given (mean of 3·3 per patient); wire-guided dilatation of the oesophagus was required before laser therapy on 159 (25 per cent) of 633 occasions. Seventy-nine (42 per cent) patients survived for 2 months, and 22 (12 per cent) survived for 6 months. Perforation of the oesophagus occurred in 12 cases. On two occasions this was secondary to laser treatment and in ten cases it was secondary to dilatation. There were 11 (6 per cent) deaths related to treatment (five secondary to perforation, three resulting from haemorrhage, and one each from a cardiovascular accident, aspiration pneumonia and an oesophagopleural fistula). In addition, seven other patients had an oesophageal perforation which responded to conservative management.

The dysphagia index for all patients showed an improvement from a median of 3 (range 0–4) before treatment to 1 (range 0–4) with treatment. This improvement was maintained for 6 months (Wilcoxon signed rank test, $P<0·001$) (*Table 1*). Overall, 172 (91 per cent) patients benefited from treatment (dysphagia index $\leqslant 2$).

The pattern of swallowing in patients who survived for more than 2 months (42 per cent of the total) is shown in *Table 2*. This demonstrates that satisfactory swallowing can be maintained in the long term by laser therapy alone in 89 per cent (70 of 79) of cases.

Various factors were investigated to determine whether they

Table 1 *Dysphagia indices in 189 patients with malignant dysphagia*

	Before treatment	Time after treatment (months)			
		1	2	4	6
All patients	3 (0–4)	1 (0–4)	1 (0–4)	1 (0–4)	1 (0–4)
Tumour length					
< 5 cm	3 (0–4)	1 (0–4)	1 (0–4)	1 (0–3)	1 (0–3)
⩾ 5 cm	3 (0–4)	1 (0–3)	1 (0–4)	1 (0–4)	1 (0–4)
Tumour site					
Stomach	3 (0–4)	1 (0–3)	1 (0–4)	1 (0–2)	1 (0–3)
Oesophagus					
Lower third	3 (1–4)	1 (0–4)	1 (0–3)	1 (0–4)	1 (0–4)
Upper two-thirds	3 (2–4)	2 (0–4)	1 (0–4)	1 (0–3)	1 (1–3)
Histological type					
Adenocarcinoma	3 (0–4)	1 (0–4)	1 (0–4)	1 (0–4)	1 (0–4)
Squamous carcinoma	3 (2–4)	2 (0–4)	1 (0–4)	1 (1–3)	1 (0–3)

Values are medians with ranges in parentheses

Table 2 *Pattern of swallowing in 79 patients who survived for more than 2 months*

	No. of patients
Good and well maintained	40 (51)
Good with occasional (⩽2) lapses	12 (15)
Good initially with relapse of dysphagia	18 (23)
No improvement, required intubation	9 (11)

Values in parentheses are percentages

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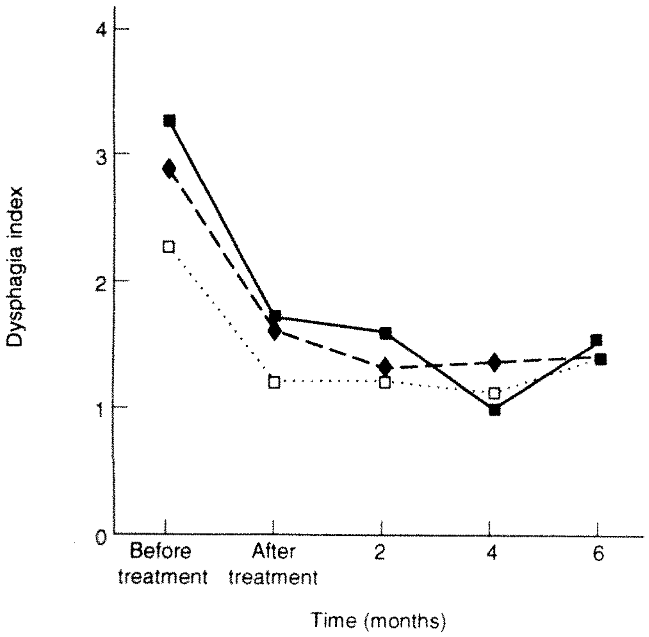

Figure 1 *Mean dysphagia indices in patients with tumours in the stomach* (□), *lower third* (◆) *and upper two-thirds* (■) *of the oesophagus*

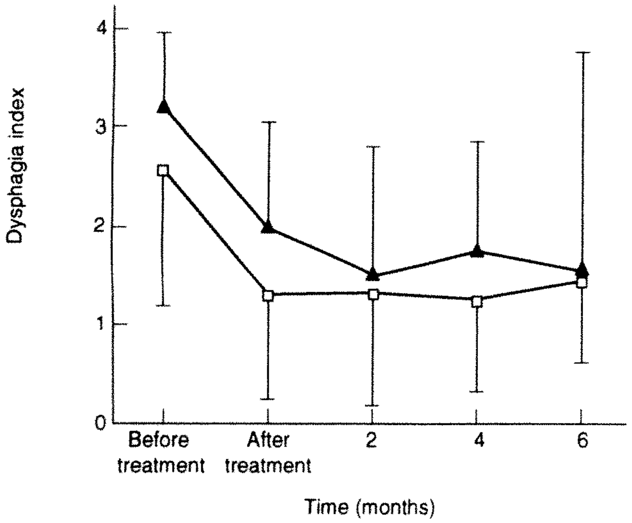

Figure 2 *Mean(s.d.) dysphagia indices in patients with adenocarcinoma* (□) *and squamous carcinoma* (▲)

influenced outcome: tumour length, histology and site (*Table 1*). There was no difference in the dysphagia index between long and short tumours at any stage (Mann–Whitney *U* test, $P>0{\cdot}1$).

Patients with tumours at various sites had more severe dysphagia on presentation if the tumour was in the upper two-thirds of the oesophagus compared with the lower third of the oesophagus or the stomach (Kruskal–Wallis analysis of variance, $P<0{\cdot}001$) (*Figure 1*). There was no difference, however, in the degree of dysphagia between any site after treatment (Kruskal–Wallis, $P>0{\cdot}1$) (*Table 1*).

Changes in the dysphagia index in patients with adenocarcinoma and squamous carcinoma are shown in *Figure 2* and *Table 1*. Patients with adenocarcinoma had better swallowing than those with squamous tumours before (Mann–Whitney *U* test, $P<0{\cdot}01$) and after ($P<0{\cdot}01$) treatment. This difference disappeared 2 months after treatment ($P>0{\cdot}1$).

The effect of histological type, tumour length and tumour site on survival is shown in *Table 3*. There was no significant difference in the survival rate at either 2 or 6 months for any factor (χ^2 test with Yates' correction, $P>0{\cdot}1$ in all cases).

Table 3 *Patient survival*

	Total no. of patients	No. surviving after treatment: At 2 months	No. surviving after treatment: At 6 months
All patients	189	79 (42)	22 (12)
Tumour length			
<5 cm	93	49 (53)	14 (15)
≥5 cm	96	42 (44)	10 (10)
Tumour site			
Stomach	89	40 (45)	9 (10)
Oesophagus			
Lower third	72	32 (46)	12 (17)
Upper two-thirds	28	13 (46)	1 (4)
Histological type			
Adenocarcinoma	145	70 (48)	20 (14)
Squamous carcinoma	39	16 (41)	2 (5)

Values in parentheses are percentages

Discussion

These findings for overall benefit and maintenance of swallowing are in agreement with those of other workers[2,3], and illustrate the appalling prognosis in this disease.

The alternative to laser therapy in providing palliation for these patients is intubation. In recent studies comparing these two modalities of treatment, they both appear to be equally effective at relieving dysphagia. Normal swallowing can be achieved only with the laser, however, and intubation is associated with a higher incidence of complications[5,6]. It is our experience that intubation never produces a dysphagia grade of less than 2. The risk of perforation (6 per cent per patient or 2 per cent per treatment) is largely related to dilatation rather than laser treatment, and compares favourably with that seen with intubation[7].

It has been suggested that laser therapy is better for intrinsic tumours and intubation for intramural or extrinsic disease[6]. It is impossible to categorize more than a few patients into these groups because more than 90 per cent of cases had both intraluminal and intramural components.

It was hoped that this study would enable identification of endoscopic features that would predict which patients would do well with laser treatment, and which would not. The latter could then receive immediate intubation. It has not been possible to identify any such prognostic features. All patients are therefore treated initially with laser therapy as this technique can sometimes result in normal swallowing. Intubation is reserved for those patients who have no relief of dysphagia with the laser.

References

1. Muller JM, Erasmi H, Stelzner M *et al.* Surgical therapy of oesophageal carcinoma. *Br J Surg* 1990; **77**: 845–57.
2. Krasner N, Barr H, Skidmore C *et al.* Palliative laser therapy for malignant dysphagia. *Gut* 1987; **28**: 792–8.
3. Bown S, Hawes E, Matthewson K *et al.* Endoscopic laser palliation for advanced malignant dysphagia. *Gut* 1987; **28**: 799–807.
4. Houghton A, Mason R, Allen A *et al.* NdYAG laser treatment in the palliation of advanced oesophageal malignancy. *Br J Surg* 1989; **76**: 912–13.
5. Alderson D, Wright PD. Laser recanalization *versus* endoscopic intubation in the palliation of malignant dysphagia. *Br J Surg* 1990; **77**: 1151–3.
6. Barr H, Krasner N, Raouf A *et al.* Prospective randomised trial of laser therapy only and laser therapy followed by endoscopic intubation for the palliation of malignant dysphagia. *Gut* 1990; **31**: 252–8.
7. Lishman DH, Dellipani AW, Devlin HB. The insertion of oesophagogastric tubes in malignant strictures: endoscopy or surgery. *Br J Surg* 1980; **67**: 257–9.

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Transhiatal oesophagectomy for oesophageal carcinoma

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Between 1979 and 1990 transhiatal oesophagectomy and reconstruction with stomach was performed in 148 patients with carcinoma of the oesophagus. Ninety-seven patients were men and 51 were women; ages ranged from 21 to 88 years with a mean of 57·4 years. Dysphagia and weight loss were the usual clinical symptoms. The mean duration of symptoms was 14 weeks. Squamous cell carcinoma was present in 129 patients (87·2 per cent), 18 patients (12·2 per cent) had adenocarcinoma, and one had lymphoma (0·7 per cent). In two-thirds of the patients tumours were located in the middle thoracic (50 of 148 patients) or distal thoracic oesophagus (59 of 148 patients). Three-quarters of the patients had tumours determined as stage III. The mean length of hospital stay after operation was 12·8 days. Anastomotic leakage occurred in 15 cases (10·1 per cent). Pulmonary complications other than pneumothorax were observed in 36 cases (24·3 per cent). The 30-day postoperative mortality rate was 8·1 per cent (12 of 148 patients). Respiratory insufficiency was observed as the major cause of death (six of 12 patients). Mediastinitis due to necrosis of the transposed stomach in the mediastinum was the cause of death in three cases. Two-year actuarial survival rates in patients with cervical, upper, middle and lower thoracic tumours were 20, 22, 26 and 30 per cent respectively. Transhiatal oesophagectomy is safe and offers limited morbidity and mortality, although pulmonary complications and anastomotic leakage in the early postoperative period still pose a significant risk, especially for elderly patients in poor condition.

Patients with oesophageal carcinoma are often elderly and have poor nutritional and pulmonary status. Blunt transhiatal oesophagectomy is advocated for these patients to reduce morbidity and mortality rates. This technique has been applied to tumours at all levels of the oesophagus[1–8]. Transhiatal oesophagectomy is a safe, short and physiologically well tolerated technique associated with less blood loss and a lower incidence of pulmonary complications than in the standard transthoracic approach for carcinoma of the oesophagus[6]. The complications of this procedure are few and can be treated easily[3].

One major disadvantage of the procedure is that it has been reported as an inadequate operation for cancer. Thus, some authors prefer radical transthoracic oesophagectomy for the treatment of oesophageal carcinoma[9,10]. Despite the improvements in care before and after operation, a combined thoracoabdominal procedure in these patients may entail extremely high morbidity and mortality rates[1,11].

Some authors have compared oesophagectomy with and without thoracotomy[12,13]. Blunt transhiatal oesophagectomy avoids respiratory complications associated with a thoracotomy incision and removes the risk of mediastinitis from an intrathoracic anastomotic leakage.

For the past 10 years, transhiatal oesophagectomy and reconstruction with stomach has been the usual operative approach in our clinic[14,15]. This report reviews our experience of 148 patients with oesophageal carcinoma analysed according to morbidity, mortality and survival rates.

Patients and methods

Between 1979 and 1990, 148 patients with carcinoma of the oesophagus underwent transhiatal oesophagectomy and reconstruction with stomach. This was our standard approach during this period for oesophageal carcinoma. Patients with tumours of the cardia that infiltrated the fundus of the stomach and who underwent transthoracic oesophagectomy with intrathoracic oesophagogastric anastomosis and patients with irresectable tumours in whom other procedures were performed have been excluded. Between 1965 and 1990, 1125 patients with carcinoma of the oesophagus were admitted to our clinic. Of these, 488 (43·4 per cent) patients were irresectable. The operative approaches performed in 637 (56·6 per cent) cases considered as resectable were as follows: transthoracic oesophagectomy and gastric reconstruction, 178 cases; transthoracic oesophagectomy and colonic reconstruction, 227 cases; transthoracic oesophagectomy and jejunal reconstruction, 62 cases; transhiatal oesophagectomy and reconstruction with stomach, 148 cases; and cervical jejunal autograft interposition, 22 cases.

Of those who underwent transhiatal oesophagectomy there were 97 men (65·5 per cent) and 51 women (34·5 per cent) (M:F ratio 1·9:1). The ages of the patients ranged from 21 to 88 years with a mean of 57·4 years (*Figure 1*). One hundred and six patients (71·6 per cent) were aged over 50 years. Dysphagia and weight loss were the usual symptoms. Twenty-four patients had dysphagia for less than 30 days, 105 patients for between 1 and 6 months, and the remaining 19 patients had dysphagia for more than 6 months before the diagnosis of oesophageal carcinoma. The mean duration of symptoms was 14 weeks.

Tumours were located in the cervical oesophagus in 24 (16·2 per cent) patients, in the upper thoracic oesophagus in 15 (10·1 per cent) patients, in the middle thoracic part in 50 (33·8 per cent), and in the lower part of the oesophagus in 59 (39·9 per cent) patients. Squamous cell carcinoma was present in 129 (87·2 per cent) cases, adenocarcinoma in 18 (12·2 per cent) cases and lymphoma in one (0·7 per cent) case. One hundred and twelve (75·7 per cent) cases were in stage III, 32 cases were in stage II (21·6 per cent), three cases were in stage IV (2·0 per cent) and only one case was in stage I (0·7 per cent)[16].

Preoperative management

After physical examination, investigation included routine haematological and biochemical tests, electrocardiography, liver and lung function tests, and arterial blood gas analysis. Localization and possible spread of the tumour was investigated by chest radiography, barium

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This work was presented at the 1st Eurosurgery Congress, held on 1–4 October 1990 in Paris, France

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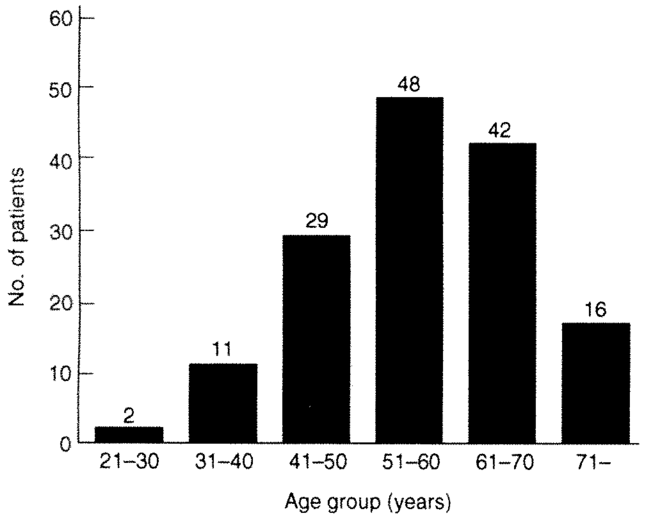

Figure 1 *Age distribution of 148 patients with oesophageal malignancy treated by transhiatal oesophagectomy*

swallow, endoscopy and biopsy in all cases. Indirect laryngoscopy and bronchoscopy were performed as indicated by symptoms. Ultrasonographic examination of the liver and coeliac lymph nodes was performed routinely, but computed tomography (CT) was performed only in the last 48 cases. Parenteral nutrition was administered before operation if the serum albumin level was less than 3·0 g/l.

Operation

Transhiatal oesophagectomy with cervical oesophagogastrostomy was performed in all patients. The stomach was passed through the posterior mediastinum in the original oesophageal bed. During the preparation of the stomach in tubular form, the vascular arcade of the greater curvature was maintained to the level of the short gastric vessels. The anastomosis was made in the cervical region with a hand-sewn technique using two layers of sutures. A chest drain was inserted intraoperatively if pleural rupture was observed during the procedure. Antibiotic prophylaxis was administered to all patients perioperatively.

Postoperative management

Nasogastric tube decompression and infusion of saline and dextrose solutions or parenteral nutrition were used in all cases. Total parenteral nutrition delivered 3000 kcal/day (12·5 MJ/day). On the seventh day after operation, before commencing oral feeding, anastomotic integrity was studied by radiographic examination with Gastrografin® (Schering AG, Berlin, Germany). Clinical leakage, associated with local and systemic signs of sepsis, was diagnosed when there was discharge of saliva or food substance through the cervical wound. In addition, when the radiological examination revealed contained extravasation of the contrast in an asymptomatic patient, the leakage was defined as subclinical. Patients with stage III and IV tumours received radiotherapy after discharge from our clinic.

Statistical analysis

Survival curves were constructed by the Kaplan–Meier method[17].

Results

No intraoperative deaths were recorded. The mean operative blood loss was 898 ml (range 550–1800 ml). The mean length of hospital stay after operation was 12·8 days.

Intraoperative complications

Sixty-six (44·6 per cent) cases had pneumothorax due to rupture of the pleura during transhiatal blunt resection of the oesophagus. This minor complication was treated by introducing a chest drainage tube(s) and establishing an underwater seal drain system. Tracheal or bronchial tear was not observed in our series. Ten patients required splenectomy following intraoperative injury to the spleen. A thoracotomy for intrathoracic haemorrhage was not required in any case. Eleven (7·4 per cent) patients developed hoarseness due to injury to the recurrent laryngeal nerve.

Postoperative complications

Table 1 shows the postoperative complications. Anastomotic leakage occurred in 15 (10·1 per cent) cases between 3 and 16 days (mean 8·4 days) after operation. Ten cases were designated as clinical leaks and the others were established as subclinical. All patients had total parenteral nutrition in the initial phase of management. Enteral feeding by nasogastric tube was substituted for parenteral nutrition in four patients who had prolonged fistulae. One patient had a persistent fistula due to recurrence of the tumour which did not respond to conservative treatment. One patient died from a cerebrovascular embolus during conservative treatment of a fistula. The fistulae closed spontaneously in the other eight patients.

Eleven (7·4 per cent) cases of this series developed anastomotic stenosis which was treated by mechanical dilatation after operation. Pyloric stenosis occurred in four (2·7 per cent) cases, and wound infection was observed in four (2·7 per cent) cases.

Postoperative pulmonary complications occurred in 36 (24·3 per cent) cases (*Table 1*). Eight (5·4 per cent) cases had respiratory infection which was diagnosed as a febrile episode that was accompanied by radiological evidence of pneumonia. Pleural effusion was observed in ten (6·8 per cent) cases. Minimal serous effusions were treated conservatively while clinically symptomatic effusions were treated by surgical drainage. Severe atelectasis requiring mechanical ventilation occurred in 11 (7·4 per cent) cases. Acute respiratory failure developed in seven (4·7 per cent) cases, all of which were treated by endotracheal intubation and ventilatory support in the intensive care unit. Six of these patients died.

Mortality

Twelve patients died within 30 days of operation, resulting in a hospital mortality rate of 8·1 per cent. The cause of death was cerebrovascular embolus in three cases, mediastinitis in three cases, and respiratory insufficiency in six cases. The three deaths from mediastinitis occurred after necrosis of the transposed stomach in the mediastinum. No deaths were recorded from anastomotic leakage or from respiratory infection or atelectasis.

Survival

The 136 surviving patients were discharged after a mean hospitalization period after operation of 12·8 days. Two-year actuarial survival rates in patients with cervical, upper, middle and distal thoracic tumours were 20, 22, 26 and 30 per cent respectively (*Figure 2*).

Discussion

Transhiatal oesophagectomy and reconstruction with stomach can be performed for tumours at all levels of the oesophagus. This type of oesophageal resection is a safe, well tolerated and rapid technique, and the stomach is an excellent

Table 1 *Postoperative complications in 148 cases*

	No. of cases
Surgical complications	
Anastomotic leakage	15 (10·1)
Stenosis of anastomosis	11 (7·4)
Stenosis of pylorus	4 (2·7)
Wound infection	4 (2·7)
Pulmonary complications	
Acute respiratory insufficiency	7 (4·7)
Respiratory infection	8 (5·4)
Pleural effusion	10 (6·8)
Atelectasis	11 (7·4)

Values in parentheses are percentages

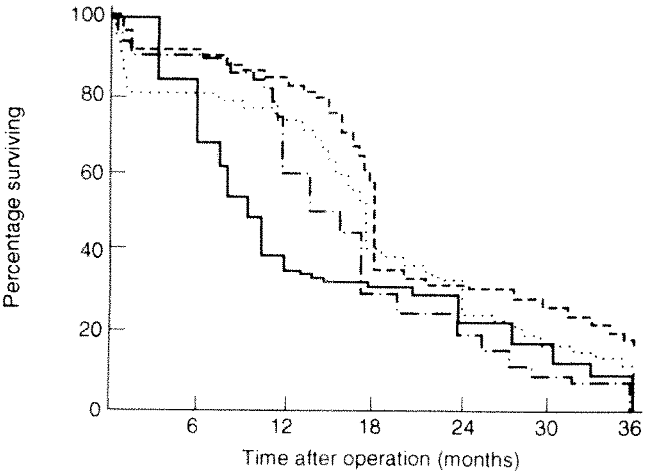

Figure 2 *Survival rates for patients with tumours located in the cervical region (— · —) and upper (——), middle (· · · · ·) and distal (-----) thirds of the thoracic oesophagus*

organ for oesophageal reconstruction, providing good function[1-3,5,14,15,18,19].

If the oesophageal carcinoma is located at the cervical or distal part of the oesophagus, transhiatal resection of the oesophagus can be performed because the tumour can be dissected under direct vision. In patients with carcinoma of the thoracic oesophagus, some technical difficulties may develop because of possible adhesions between trachea, bronchus or aorta[3,20].

In one-third of our patients, tumours were located in the middle thoracic part of the oesophagus (33·8 per cent). The use of preoperative CT of the chest in carcinoma of the oesophagus can predict extraoesophageal spread of the tumour, infiltration of surrounding tissues and resectability. This is especially true in tumours of the midthoracic oesophagus. CT has been reported to determine accurately the stage of the tumour in 88 per cent of cases and infiltration of surrounding tissues in 89 per cent. Diagnosis of lymph node metastases by CT is achieved in only 68 per cent of cases[21]. Thus, CT seems to be sensitive in identifying tracheobronchial involvement in thoracic oesophageal carcinomas. We performed CT routinely in our last 48 patients, and CT results correlated well with the postoperative histopathological findings, with accurate prediction of stage in 40 of 48 cases (83·3 per cent) (*Table 2*).

Transhiatal oesophagectomy is a more rapid procedure than thoracoabdominal resection, with less blood loss and less physiological disturbance. The reported morbidity and mortality rates with this procedure are lower than after standard transthoracic oesophagectomy[3,7,8,12,13,18,19]. The most frequent peroperative complication of transhiatal oesophagectomy is pneumothorax due to rupture of the pleura. Orringer[3] reported that this complication occurred in two-thirds of his patients, and in our series it was observed in 44·6 per cent of patients. This minor complication can be treated easily by insertion of chest drains. We have not encountered the major intraoperative complications of transhiatal oesophagectomy which are reported as tracheal laceration, chylothorax and uncontrollable haemorrhage[3]. Dissection of the oesophagus high in the neck sometimes causes injuries to the left recurrent laryngeal nerve, and occurred in 11 (7·4 per cent) of our cases.

A patient with oesophageal carcinoma who has adequate cardiorespiratory function and no evidence of distant spread can be treated palliatively by transhiatal oesophagectomy[22]. Three-quarters of our patients had tumours in stage III (75·7 per cent) and IV (2·0 per cent). Altogether, 77·7 per cent of patients in our series had palliative resections, but 22·3 per cent were treated curatively on the basis of the staging information available.

Oesophageal carcinoma occurs mainly in older patients, and concomitant disease, particularly of the cardiorespiratory system, is common. The mean age of the patients who underwent transhiatal oesophagectomy for oesophageal carcinoma was 62 years in the series reported by Orringer[3] and 65 years in the series of Barbier *et al.*[7]. In our series, the mean age was 57·4 years, but 71·6 per cent of our patients were more than 50 years old. Therefore old age cannot be claimed as a contraindication for this procedure.

The inability to eat causes a rapid weight loss, nutritional deficiency and impaired immunocompetence[19]. Malnutrition is a significant risk factor in patients undergoing major surgical procedures. The beneficial effect of preoperative parenteral nutrition on postoperative morbidity and mortality rates has been reported by some authors[23]. We administered parenteral nutrition to patients with evidence of malnutrition.

Anastomotic leakage and pulmonary complications are the most common causes of postoperative death. In one series, more anastomotic leakages were observed in bypass procedures (34·1 per cent) than in palliative (7·6 per cent) or curative resections (3·7 per cent)[19]. This complication occurred in 10·1 per cent of cases in our study. Orringer and Orringer[2] reported an anastomotic leak in 12 per cent of 143 patients, of whom 43 had benign disease. One year later, Orringer observed anastomotic leak in 5 per cent of patients with carcinoma of the thoracic oesophagus[3]. Others have reported similar figures[7]. The most serious consequence of anastomotic leakage is mediastinitis, but this is very rare after transhiatal oesophagectomy owing to the positioning of the anastomosis in the cervical region and because the transposed stomach blocks the entrance to the mediastinum. We have confirmed the low incidence of anastomotic leakage after transhiatal oesophagectomy, and the benign course of such leakage in most cases.

Respiratory complications are the other main problem after surgery for oesophageal carcinoma. Fok *et al.*[13] compared transhiatal and transthoracic resection for oesophageal carcinoma and found that pleural effusion, atelectasis and empyema thoracis occurred more frequently after a transthoracic procedure. They concluded that a transhiatal approach should reduce pulmonary complications. A surgical procedure involving an upper abdominal incision with a thoracotomy wound has been shown to produce a greater disturbance in respiratory function than abdominal incision alone[24]. Also, extended lymphadenectomy can result in stromal oedema of the lung due to interference with lymph flow[25] and can decrease the expectoration of bronchial secretions because injury to the bronchial branch of the vagus can impair the cough reflex.

The hospital mortality rate for transthoracic procedures ranges from 11 to 17·5 per cent[9,10,13,19]. The main causes of death are respiratory failure, sepsis, anastomotic leakage and malignant cachexia[13]. The operative mortality rate of transhiatal oesophagectomy has been reported to range from 1·4 to 7·7 per cent[4,5,7,11,18]. In contrast, Fok *et al.*[13] compared the 30-day mortality rate for transthoracic and transhiatal procedures and reported that the mortality rates of the two procedures were not statistically different. In our series, the hospital mortality rate was 8·1 per cent, and respiratory failure was the major cause of death (six of 12 deaths). Mediastinitis due to necrosis of the transposed stomach in the mediastinum

Table 2 *Comparison of preoperative staging by CT with postoperative histopathological staging in 48 patients*

Preoperative staging by CT	Postoperative histopathological staging			
	I	II	III	IV
Stage I ($n = 1$)	1	–	–	–
Stage II ($n = 15$)	–	11	4	–
Stage III ($n = 28$)	–	4	24	–
Stage IV ($n = 4$)	–	–	–	4

CT, computed tomography

and cerebovascular embolus were the other two causes of postoperative death.

Barbier *et al.*[8] reported a survival rate of 34 per cent at 2 years and 23 per cent at 3 years. The median survival time is reported variously as 13·1, 15·7 and 19 months[4,8,11]. In the series of Akiyama *et al.*[18] the overall 5-year survival rate was 34·6 per cent by the transthoracic procedure. Skinner[9] performed radical oesophagectomy with *en bloc* lymph node dissection for treatment of oesophageal carcinoma, and reported a 3-year actuarial survival rate of 14 per cent for midthoracic carcinomas and of 33 per cent for distal-third tumours. These results appear to offer little advantage over those obtained with transhiatal oesophagectomy. Orringer's report[3] showed a 3-year survival rate of 31 per cent for distal-third carcinomas and of 17 per cent for midthoracic carcinomas. Our 2-year survival rates in midthoracic and distal-third tumours were 26 and 30 per cent respectively.

In conclusion, transhiatal blunt oesophagectomy and reconstruction with stomach is a physiologically well tolerated technique. CT of the mediastinum should be used before operation, especially in cases with tumours of the middle and upper thoracic oesophagus. If CT demonstrates involvement of surrounding tissues such as the tracheobronchial tree, aorta or pericardium, transhiatal oesophagectomy is not suitable. This safe approach can be considered to be curative in patients with stage I and II tumours. It is a palliative procedure in stage III and IV disease, but will result in restoration of normal swallowing. Despite improvements in evaluation before operation and in care after surgery, pulmonary complications in the early postoperative period still remain a problem.

References

1. Orringer MB, Sloan H. Esophagectomy without thoracotomy. *J Thorac Cardiovasc Surg* 1978; **76**: 643–54.
2. Orringer MB, Orringer JS. Esophagectomy without thoracotomy: a dangerous operation? *J Thorac Cardiovasc Surg* 1983; **85**: 72–80.
3. Orringer MB. Transhiatal esophagectomy without thoracotomy for carcinoma of the thoracic esophagus. *Ann Surg* 1984; **200**: 282–8.
4. Tryzelaar JF, Neptune WB, Ellis FH. Esophagectomy without thoracotomy for carcinoma of the esophagus. *Am J Surg* 1982; **143**: 486–9.
5. Baker JW, Schechter GL. Management of panesophageal cancer by blunt resection without thoracotomy and reconstruction with stomach. *Ann Surg* 1986; **203**: 491–9.
6. Wong J. Transhiatal oesophagectomy for carcinoma of the thoracic oesophagus. *Br J Surg* 1986; **73**: 89–90.
7. Barbier PA, Becker CD, Wagner HE. Esophageal carcinoma: patient selection for transhiatal esophagectomy. A prospective analysis of 50 consecutive cases. *World J Surg* 1988; **12**: 263–9.
8. Barbier PA, Luder PJ, Schuepfer G, Becker CD. Quality of life and patterns of recurrence following transhiatal esophagectomy for cancer: results of a prospective follow-up in 50 patients. *World J Surg* 1988; **12**: 270–6.
9. Skinner DB. *En-bloc* resection for neoplasms of the esophagus and cardia. *J Thorac Cardiovasc Surg* 1983; **85**: 59–71.
10. Desa L, Ragnunath AS, Chawla SL, Peel ALG, Dellipiani AW. Treatment policy for the management of carcinoma of the oesophagus. *Br J Surg* 1988; **75**: 275–8.
11. Finley RJ, Grace M, Duff JH. Esophagectomy without thoracotomy for carcinoma of the cardia and lower part of the esophagus. *Surg Gynecol Obstet* 1985; **160**: 49–56.
12. Steiger Z, Wilson RF. Comparison of the results of esophagectomy with and without thoracotomy. *Surg Gynecol Obstet* 1981; **153**: 653–6.
13. Fok M, Siu KF, Wong J. A comparison of transhiatal and transthoracic resection for carcinoma of the thoracic esophagus. *Am J Surg* 1989; **158**: 414–19.
14. Gürkan N, Avci C, Terzioglu T, Sasmaz O. L'oesophagectomie sans thoracotomie dans le traitement du cancer de l'oesophage. Analyses de 47 cas. *Chirurgie* 1984; **110**: 608–14.
15. Gürkan N, Avci C, Demirkol K, Eldegez U, Terzioglu T, Sasmaz O. Experience with esophagectomy without thoracotomy in 67 cases. In: Siewert JR, Hoelscher AH, eds. *Diseases of the Esophagus*. Berlin: Springer-Verlag, 1987: 403–6.
16. Japanese Committee for Registration of Esophageal Carcinoma. A proposal for new TNM classification of esophageal carcinoma. *Jpn J Clin Oncol* 1985; **14**: 625–36.
17. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Statist Assoc* 1958; **53**: 457–81.
18. Akiyama H, Tsurumaru M, Kawamura T, Watanabe C, Ono Y. Principles of surgical treatment for carcinoma of the esophagus: analysis of lymph node involvement. *Ann Surg* 1981; **194**: 438–46.
19. Postlethwait RW. Complications and deaths after operations for esophageal carcinoma. *J Thorac Cardiovasc Surg* 1983; **85**: 827–31.
20. Goldfaden D, Orringer MB, Appelman HD, Kalish R. Adenocarcinoma of the distal esophagus and gastric cardia. *J Thorac Cardiovasc Surg* 1986; **91**: 242–7.
21. Lefor AT, Merino MM, Steinberg SM *et al.* Computerized tomographic prediction of extraluminal spread and prognostic implications of lesion width in esophageal carcinoma. *Cancer* 1988; **62**: 1287–97.
22. Hennessy TPJ. Choice of treatment in carcinoma of the oesophagus. *Br J Surg* 1988; **75**: 193–4.
23. Daly JM, Massar E, Giacco G *et al.* Parenteral nutrition in esophageal cancer patients. *Ann Surg* 1982; **196**: 203–8.
24. Bishop DGM, McKeown KC. Postoperative hypoxaemia: oesophagectomy with gastric replacement. *Br J Surg* 1979; **66**: 810–12.
25. Sugimaci K, Veo H, Natsuda Y, Kai H, Inokuchi K, Zaitsu A. Cough dynamics in oesophageal carcinoma: prevention of postoperative complications. *Br J Surg* 1982; **69**: 734–6.

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Histopathological study of oesophageal mucosa in patients with varices: a comparison between bleeders and non-bleeders

Thirty-six patients with oesophageal varices underwent a non-shunting operation including oesophageal transection. Of these, 16 had an emergency or elective operation (bleeders) and the remaining 20 had prophylactic surgery (non-bleeders). A comparative study was performed between the bleeders and non-bleeders in terms of preoperative endoscopic findings and histopathology of the oesophagus. The severity of red colour sign showed no significant difference between the two groups. The venous dilatation in each of the three layers of the oesophageal mucosa was demonstrated histologically to be of the same degree in bleeders and non-bleeders. In addition, the hepatic venous pressure gradient in cirrhotic patients did not differ between the two groups; for bleeders this was a mean(s.d.) of 15·2(6·1) mmHg and for non-bleeders 14·4(2·9) mmHg. We were unable to find any factors differentiating bleeders from non-bleeders, although these results do not justify prophylactic surgery for oesophageal varices.

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Haemorrhage from ruptured oesophageal varices is one of the most serious complications of portal hypertension. The endoscope has been used as an important diagnostic tool in assessing the severity of varices as well as in identifying the source of bleeding. In Japan, endoscopic findings of oesophageal varices are usually classified according to the general rules for recording endoscopic findings on oesophageal varices prepared by the Japanese Research Society for Portal Hypertension[1]. A retrospective study by Beppu *et al.*[2] indicated that red wall markings and cherry-red spots of the red colour sign category were positively correlated with the rate of variceal bleeding. Non-shunting procedures have been performed in Japan on the basis of these endoscopic findings in patients who have no history of bleeding from oesophageal varices. These prophylactic operations, however, are not fully justified[3]. In contrast, prophylactic portacaval shunt has been abandoned in western countries[4–8]. The main reasons are the operative mortality and morbidity rates of shunt surgery and the failure of prophylactic shunts to improve the long-term survival rate.

We report here a comparative study of prophylactic cases (non-bleeders) and emergency or elective cases (bleeders), comparing preoperative endoscopic assessment and histopathological findings of the oesophagus obtained by transection using an enteric end anastomosis (EEA) stapler.

Patients and methods

Thirty-six patients who underwent non-shunting operation[9] were studied; 24 men and 12 women with a mean(s.d.) age of 56·8(6·9) years. Of these, 16 (13 liver cirrhosis, three idiopathic portal hypertension) underwent emergency or elective transection (bleeders) and 20 (13 liver cirrhosis, five idiopathic portal hypertension, two extrahepatic portal obstruction) had prophylactic operation (non-bleeders). Liver biopsy was peformed during the operation in each case.

No patient had undergone endoscopic sclerotherapy within 1 year of surgery, although four of the 16 bleeders had a previous history of injection sclerotherapy. In all cases endoscopic examination was performed within 40 days (mean(s.d.) 20·1(13·7) days) before operation using a flexible endoscope. The oesophageal mucosa in the distal 5 cm of the oesophagus was inspected to document the features according to the general rules for recording endoscopic findings on oesophageal varices[1].

With regard to the size of varices, the rules include three degrees: small straight varices (F$_1$); enlarged tortuous varices occupying less than one-third of the oesophageal lumen (F$_2$); coil-shaped varices occupying more than one-third of the oesophageal lumen (F$_3$). In this study the red colour sign on the variceal surface was artificially divided into a minor degree in which both red wall markings and cherry-red spots were negative or mild (+), and a major degree, in which both red wall markings and cherry-red spots were moderate (++) or severe (+++).

Prophylactic transections were performed for patients who had both F$_2$ or F$_3$ size varices and positive endoscopic red colour sign. The oesophageal transection was performed transabdominally[9,10] using an EEA stapler. A full-thickness oesophageal ring was obtained, fixed in mercuric formalin solution and stained with haematoxylin and eosin. Sections were taken along the longitudinal axis of the oesophagus. One pathologist 'blindly' reviewed the histological sections. The degree of venous dilatation of each of the three layers of the oesophagus (the squamous epithelium, mucosa propria and submucosa) was graded according to the maximum diameter of dilated veins as follows: (1) in the squamous epithelium, 'marked' means the maximum diameter of dilated veins is $>0·50$ mm, 'moderate' means $\leq 0·50$ mm, and 'unremarkable' indicates an absence of veins; (2) in the mucosa propria, 'marked' means $>0·50$ mm, 'moderate' 0·15–0·50 mm, and 'unremarkable' $<0·15$ mm; (3) in the submucosa, 'marked' means $>1·00$ mm, 'moderate' 0·50–1·00 mm, and 'unremarkable' $<0·50$ mm (*Figures 1* and *2*). These classifications were based on the finding that in six patients who underwent total gastrectomy for stomach cancer using an EEA stapler, there was an absence of veins in the squamous epithelium, and the maximum diameter of veins in the mucosa propria was $<0·15$ mm, and in the submucosa $<0·50$ mm (unpublished data).

Hepatic venous pressure was measured before operation under local anaesthesia with an 8 Fr balloon-tipped catheter (Johnson–Johnson Company, Tampa, Florida, USA) placed in the main right hepatic vein. Wedged and free hepatic venous pressures were obtained by inflating and releasing the balloon. The gradient between the wedged and free hepatic venous pressures is termed the hepatic venous pressure gradient (HVPG). Patients with idiopathic portal hypertension and extrahepatic portal obstruction were excluded from the HVPG study, since HVPG does not reflect portal venous pressure in these cases. For patients with liver cirrhosis, HVPG was measured in 10 of 13 bleeders and in all 13 non-bleeders.

Statistical comparison was performed using the Wilcoxon test or the Student's *t* test for unpaired data.

Results

Endoscopic findings before operation

Fourteen of the 16 bleeders and 15 of the 20 non-bleeders had

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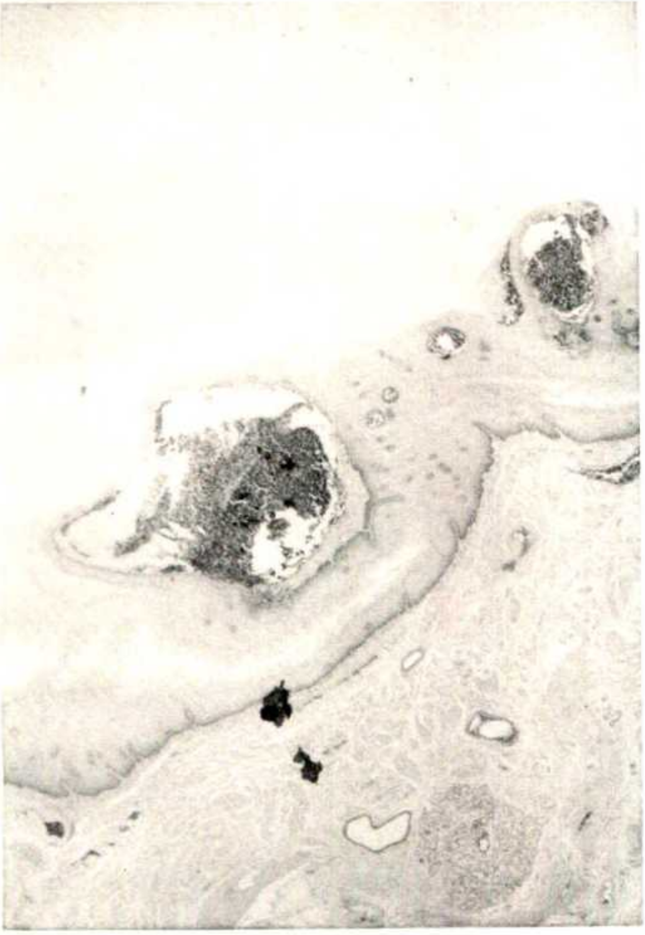

Figure 1 *Several markedly dilated blood-filled channels within the oesophageal squamous epithelium in a patient with portal hypertension (haematoxylin and eosin stain, original magnification × 40)*

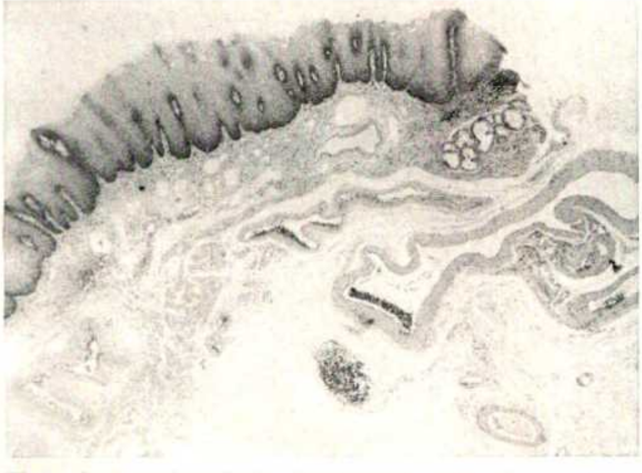

Figure 2 *Several markedly dilated vessels within the oesophageal submucosa in a patient with portal hypertension (haematoxylin and eosin stain, original magnification × 40)*

severe red colour sign. F_2 or F_3 varices were demonstrated in all bleeders and in all but one of the non-bleeders (*Table 1*). There was no statistically significant difference in endoscopic findings between the two groups ($P > 0{\cdot}10$; Wilcoxon test for unpaired data).

Hepatic venous pressure gradient

When the HVPG in patients with liver cirrhosis was assessed, there was no statistically significant difference between emergency or elective cases (bleeders) and prophylactic cases: mean(s.d.) HVPG was 15·2(6·1) mmHg and 14·4(2·9) mmHg respectively (*Figure 3*).

Histopathological study of oesophagus

A sufficient oesophageal specimen could not be obtained for histopathological investigation in five patients, since each specimen obtained in those cases consisted mainly of gastric rather than oesophageal mucosa. The remaining 31 cases (14 bleeders and 17 non-bleeders) were studied. The mean(s.d.) distance between the oesophagogastric junction and transected portion was 2·6(0·5) cm and the mean(s.d.) oesophageal ring width was 0·8(0·3) cm. With respect to the squamous epithelium, the number of patients with moderate venous dilatation was 11 of 14 (79 per cent) in bleeders and 11 of 17 (65 per cent) in non-bleeders. There was no patient without venous dilatation in the mucosa propria in either group. In the submucosal layer, there was either moderate or severe venous dilatation in all patients. These results indicate that there was no statistically significant difference between bleeders and non-bleeders with regard to histopathological findings (*Table 2*).

Table 1 *Endoscopic findings in emergency or elective cases (bleeders) and prophylactic cases (non-bleeders)*

	Bleeders ($n = 16$)	Non-bleeders ($n = 20$)
Red colour sign		
Minor degree	2	5
Major degree	14	15
Size*		
F_1	0	1
F_2	5	11
F_3	11	8

*For definitions of size, see text

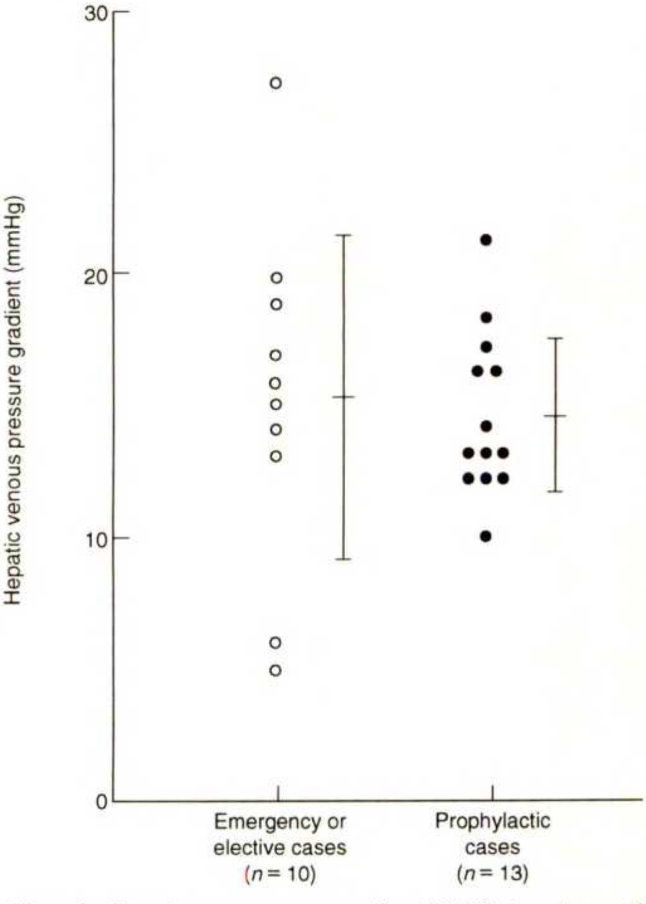

Figure 3 *Hepatic venous pressure gradient (HVPG) in patients with liver cirrhosis. Bars indicate mean and standard deviation. There was no statistically significant difference between emergency or elective cases and prophylactic cases (Student's* t *test for unpaired data)*

Table 2 *Venous dilatation of each layer of the oesophageal mucosa*

Venous dilatation*	Bleeders ($n = 14$)	Non-bleeders ($n = 17$)
Squamous epithelium		
Unremarkable	2	3
Moderate	11	11
Marked	1	3
Mucosa propria		
Unremarkable	0	0
Moderate	2	5
Marked	12	12
Submucosa		
Unremarkable	0	0
Moderate	2	4
Marked	12	13

*For definitions, see text

Table 3 *Comparison between red colour sign and venous dilatation in the oesophageal mucosa*

	Red colour sign	
Venous dilatation*	Minor degree ($n = 7$)	Major degree ($n = 24$)
Squamous epithelium		
Unremarkable	4	1†
Moderate	3	19†
Marked	0	4†
Mucosa propria		
Unremarkable	0	0
Moderate	3	4
Marked	4	20
Submucosa		
Unremarkable	0	0
Moderate	1	5
Marked	6	19

*For definitions, see text. †$P < 0{\cdot}05$ (patients with a major degree of red colour sign *versus* patients with a minor degree of red colour sign, Wilcoxon test for unpaired data)

Comparison between pathological and endoscopic findings

As shown in *Table 3*, venous dilatation in the squamous epithelium of patients with a major degree of red colour sign was significantly more marked ($P < 0{\cdot}05$) than in the epithelium of those with a minor degree of red colour sign. On the other hand, venous dilatation in the propria and submucosa seemed moderate or marked in all patients, regardless of the severity of red colour sign.

Discussion

The bleeding source of ruptured oesophageal varices can usually be identified in the distal 5 cm of the oesophagus at autopsy or from endoscopic and surgical studies[10,11]. During oesophageal transection with the EEA stapling instrument a full-thickness ring of oesophagus is excised, followed by an immediate stapled anastomosis. In this way, we were able to obtain an oesophageal ring at a mean of 2·6 cm above the oesophagogastric junction, and this specimen allowed study of the pathological features of the oesophageal portion where variceal rupture most frequently occurs. The degree of venous dilatation in each of the three oesophageal layers did not show any significant difference between bleeders and non-bleeders.

It remains unclear how oesophageal varices rupture[12]. Viallet[13] and Garcia-Tsao *et al.*[14] found that the risk of bleeding was low or absent when the HVPG was <12 mmHg. In the present study the HVPG was >12 mmHg in most of the cirrhotic patients in both groups (eight of ten bleeders; 12 of 13 non-bleeders).

Among endoscopic findings, red colour sign is one of the most important factors predicting oesophageal variceal bleeding[2]. Spence *et al.*[15,16] found venous dilatation in the squamous epithelium in all cases in their study of oesophageal rings obtained by emergency or elective transection. They postulated that these intraepithelial channels seen at microscopic examination might represent the cherry-red spots and the red wall markings. In the present study intraepithelial venous dilatation was found in 87 per cent of cases. The severity of red colour sign on preoperative endoscopy seemed to correlate with the degree of venous dilatation in the oesophageal epithelium.

It is of interest that there was no significant difference between bleeders and non-bleeders in terms of endoscopic or histopathological findings in the oesophagus within 5 cm of the oesophagogastric junction, where variceal rupture occurs most frequently. The HVPG, reflecting variceal pressure, also did not differ between bleeders and non-bleeders.

It is uncertain from this study whether oesophageal varices in the prophylactic cases would have bled without operation or whether other important factors causing variceal rupture exist.

In conclusion, we were unable to find any factors differentiating bleeders from non-bleeders; these results cannot be used to justify prophylactic operation for patients with oesophageal varices.

References

1. Japanese Research Society for Portal Hypertension. The general rules for recording endoscopic findings on esophageal varices. *Jpn J Surg* 1980; **10**: 84–7.
2. Beppu K, Inokuchi K, Koyanagi N *et al.* Prediction of variceal hemorrhage by esophageal endoscopy. *Gastrointest Endosc* 1981; **27**: 213–18.
3. Inokuchi, K. Prophylactic portal nondecompression surgery in patients with esophageal varices. An interim report. *Ann Surg* 1984; **200**: 61–5.
4. Conn HO, Lindenmuth WW. Prophylactic portacaval anastomosis in cirrhotic patients with esophageal varices. *N Engl J Med* 1965; **272**: 1255–63.
5. Garceau AJ, Donaldson RM, O'Hara ET, Callow AD, Muench H, Chalmers TC. A controlled trial of prophylactic portacaval shunt surgery. *N Engl J Med* 1964, **270**: 496–500.
6. Jackson FC, Perrin EB, Smith EG *et al.* A clinical investigation of the portacaval shunt. *Am J Surg* 1968; **115**: 22–42.
7. Conn HO, Lindenmuth WW. Prophylactic portacaval anastomosis in cirrhotic patients with esophageal varices. *N Engl J Med* 1968; **279**: 725–32.
8. Resnich RH, Chalmers TC, Ishihara AM *et al.* A controlled study of the prophylactic portacaval shunt: a final report. *Ann Intern Med* 1969; **70**: 675–88.
9. Idezuki Y, Sanjo K. Twenty-five-year experiences with esophageal transection for esophageal varices. *J Thorac Cardiovasc Surg* 1989; **98**: 876–83.
10. Wexler MJ. Treatment of bleeding esophageal varices by transection with the EEA stapling instrument. *Surgery* 1980; **88**: 406–16.
11. Spence RAJ, Terblanche J. Venous anatomy of the lower oesophagus: a new perspective on varices. *Br J Surg* 1987; **74**: 659–60.
12. Reynolds TB. Why do varices bleed? In: Westaby D, MacDougall BRD, Williams R, eds. *Variceal Bleeding*. London: Pitman, 1982: 3–12.
13. Viallet A. Hemodynamic evaluation of patients with intrahepatic portal hypertension. *Gastroenterology* 1975; **69**: 1297–1300.
14. Garcia-Tsao G, Grossmann RJ, Fisher RL, Conn HO, Atterbury CE, Glickman M. Portal pressure, presence of gastroesophageal varices and variceal bleeding. *Hepatology* 1985; **5**: 419–24.
15. Spence RAJ, Sloan JM, Johnston GW. Histologic factors of the esophageal transection ring as clues to the pathogenesis of bleeding varices. *Surg Gynecol Obstet* 1984; **159**: 253–9.
16. Spence RAJ, Sloan JM, Johnston GW. Oesophageal mucosal changes in patients with varices. *Gut* 1983; **24**: 1024–9.

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Staple-line erosion: a common source of recurrent bleeding following stapled oesophageal transection

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Recurrent bleeding after stapled oesophageal transection was studied in 73 patients with cirrhosis transected for acute variceal bleeding. The most frequent source of bleeding was partial or total circumferential oesophageal erosion at the transection: staple-line erosion. This lesion occurred in 36 (49 per cent) patients and was the source of rebleeding in 29 (40 per cent) patients with 54 episodes. Rebleeding in 22 (30 per cent) patients was due to varices in nine (12 per cent), peptic ulcer in six (8 per cent), gastric erosions in two (3 per cent) and unknown sources in five (7 per cent), accounting for 33 episodes. The mean(s.e.m.) blood transfusion requirement for bleeding from staple-line erosions was 1·5(0·25) units per bleed versus *other sources, 6·5(1·0) units per bleed* ($P<0\cdot001$). *Staple-line erosion was present at the first postoperative endoscopy in 11 (15 per cent) patients but the time to appearance varied widely. The lesion was more common in patients with Pugh's grade A liver disease at the time of transection, reflecting the increased survival rate of these patients. Staple-line erosion is a common source of minor recurrent bleeding following stapled oesophageal transection.*

Oesophageal transection using mechanical stapling instruments is an effective treatment for bleeding oesophageal varices[1–4]. The role of stapled oesophageal transection in the emergency situation has been questioned[5] but randomized studies have shown that this procedure and emergency sclerotherapy are equally effective and have similar mortality rates in the treatment of acute variceal bleeding[6–9]. The value of oesophageal transection as a salvage procedure following failed endoscopic injection sclerotherapy is uncertain[10].

Rebleeding following stapled oesophageal transection occurs in 40–50 per cent of patients[11,12] and is ascribed to varices in about 20 per cent[5,8,11,13,14]. After endoscopic injection sclerotherapy, variceal rebleeding is more common (up to 48·6 per cent)[8]. Other sources of recurrent bleeding must account for rebleeding following stapled oesophageal transection. Oesophagitis and gastric erosions were the most frequent sources in one large series in which 40 per cent of patients suffered recurrent non-variceal rebleeding following transection[11].

This paper reports experience with recurrent bleeding in 73 patients with cirrhosis transected for acute variceal bleeding when conservative measures or emergency sclerotherapy had failed.

Patients and methods

Stapled oesophageal transection for acute variceal bleeding was performed in 73 patients over a 96-month period between January 1982 and December 1989. Emergency stapled oesophageal transection was performed as part of a trial of transection *versus* injection sclerotherapy in acute variceal bleeding not controlled by transfusion or vasoactive drugs[6] or after failed emergency sclerotherapy.

The operation was performed through a left subcostal incision as described previously[14]. An EEA® (Auto Suture UK, Ascot, UK) circular stapling instrument fitted with either a 28 mm or 31 mm diameter staple cartridge was used. The left gastric vein was not ligated and para-oesophageal devascularization was not performed. Endoscopic follow-up took place between 4 and 6 weeks after surgery and at any time in the event of recurrent upper gastrointestinal bleeding.

Patient characteristics and Pugh's gradings[15] at the time of surgery are given in *Table 1*. Sources of recurrent bleeding after stapled oesophageal transection were identified and the clinical features of the patients with rebleeding were recorded prospectively.

Results

Rebleeding following transection (Table 2)

The most frequent source of rebleeding was a total or partial circumferential oesophageal erosion identified endoscopically at the level of the transection: staple-line erosion. The diagnosis of bleeding from staple-line erosion was made on the first pass of the endoscope as passage of the instrument may have denuded the mucosa of the ring of the anastomosis to cause bleeding.

Rebleeding from staple-line erosion. This lesion was the source of 54 episodes of rebleeding in 29 (40 per cent) of the 73 patients, and was identified in seven other patients without rebleeding. The overall incidence of staple-line erosion was 49 per cent (36 patients).

Rebleeding from other sources. Eleven of the 29 patients with rebleeding from staple-line erosion also bled from other lesions: gastric or oesophageal varices (five), peptic ulcer (three), gastric

Table 1 *Characteristics of 73 patients undergoing stapled oesophageal transection*

Mean (range) age (years)	56·3 (34–83)
Sex ratio (M:F)	40:33
Pugh's grade	
A	19
B	27
C	27
Pathology	
Alcoholic cirrhosis	35
Biliary cirrhosis	13
Cryptogenic cirrhosis	17
Chronic active hepatitis	8

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Table 2 *Rebleeding following transection in 73 patients*

	Staple erosion ($n=36$)	No staple erosion ($n=37$)	Total
No. of rebleeding patients (%)	29 (40)	11 (15)	40 (55)
Source of rebleeding			
Staple-line erosion alone	18	–	18
Staple-line erosion + other	11	–	11
Other alone	–	11	11
Total	29	11	40
Other sources			
Varices	5	4	9
Peptic ulcer	3	3	6
Gastric erosions	1	1	2
Unknown	2	3	5
Total	11	11	22*
Rebleeding episodes			
Staple-line erosion	54	–	54
Other sources			
Varices	13	4	17
Peptic ulcer	6	3	9
Gastric erosions	1	1	2
Unknown	2	3	5
Total	22	11	33
Total	76	11	87

*Eleven patients with bleeding from staple-line erosion also bled from other sources

Table 3 *Blood transfusion requirements for rebleeding following transection*

Source	Episodes	Mean(s.e.m.) no. of units per bleed	Range (units/bleed)
Staple erosion	54	1·5(0·25)*	0–7
Other sources	33	6·5(1·0)	0–25
Varices	17	5·5(2·9)	0–17
Peptic ulcer	9	10·1(2·9)	3–25
Gastric erosions	2	6·5(0·5)	6–7
Unknown	5	1·4(0·7)	0–4

*$P<0·001$ *versus* other sources

erosions (one) and unknown (two), accounting for a further 22 episodes of rebleeding. There were therefore 33 episodes of rebleeding from sources other than staple-line erosion in 22 patients (30 per cent).

Blood transfusion requirements for rebleeding following transection are given in *Table 3*.

Features of staple-line erosion (Table 4)

Staple-line erosion accounted for the majority of rebleeding episodes, as shown in *Table 2*. Although staple-line erosion was present at the first endoscopy in 11 (31 per cent) of the 36 patients with staple-line erosion, the time from transection to the appearance of staple-line erosion varied greatly (mean(s.e.m.) 53(11·8) weeks; range 0·5–212 weeks). Thirty-six patients (49 per cent) died during the period of study and, when related to Pugh's grade at the time of stapled oesophageal transection, included: two (11 per cent) of 19 grade A, 11 (41 per cent) of 27 grade B, and 23 (85 per cent) of 27 grade C patients.

Similar numbers of patients with and without staple-line erosion had undergone sclerotherapy before and after stapled oesophageal transection, as shown in *Table 4*. Oesophageal staples were often visible at endoscopy following transection, but staple protrusion was not a common feature and was not identified as a 'cause' of bleeding.

One patient with rebleeding from staple-line erosion and varices underwent an elective portal systemic shunt for bleeding gastric varices but continued to bleed from the staple-line erosion after shunt surgery.

Discussion

In this series of patients with cirrhosis transected for acute variceal bleeding, just over half (55 per cent) rebled following surgery, a rate similar to that described by Wannamaker *et al.*[12]. Oesophageal varices recurred in 83 per cent of survivors of stapled oesophageal transection followed for between 6 and 43 months[13] and recurred or enlarged in 57 per cent of survivors of stapled oesophageal transection and devascularization during a mean follow-up period of 20 months[16]. In this series, however, rebleeding from recurrent varices occurred in only nine (12 per cent) patients accounting for 17 (20 per cent) rebleeding episodes following transection. This is in keeping with the recurrent variceal rebleeding rate of approximately 20 per cent in survivors of stapled oesophageal transection reported by others[5,8,11,13,14].

Staple-line erosion was the most frequent source of rebleeding in this series, occurring in 29 (40 per cent) patients and accounting for 62 per cent of rebleeding episodes.

This lesion has been poorly recognized and staple-line erosion has not been cited as a major source of rebleeding after transection. Recurrent bleeding following stapled oesophageal transection may have been misclassified or perhaps minor rebleeding from staple-line erosion was ignored. Differences in surgical techniques in performing transection may explain different incidences of staple-line erosion. Spence and Johnston[11], who used para-oesophageal devascularization and left gastric vein ligation, reported frequent minor recurrent upper gastrointestinal bleeding in almost 40 per cent of their patients followed for 5 years after transection. They identified the most frequent sources as oesophagitis and gastric erosions, but staple-line erosion may have been present. Cello *et al.*[7], Huizinga *et al.*[8] and Teres *et al.*[9] did not identify staple-line erosion, and rebleeding may have been attributed to other sources. Descriptions of oesophagitis and oesophageal ulceration seen at endoscopy following stapled oesophageal transection by Purri *et al.*[17] may include patients with staple-line erosion in whom the lesion was not specifically sought.

Table 4 *Features of staple-line erosion*

	Staple-line erosion ($n = 36$)	No staple-line erosion ($n = 37$)
Mean (range) age (years)	54·1 (34–79)	58·5 (35–83)
Sex ratio (M:F)	24:12	16:21
Pugh's grade (at transection)		
A	18	1
B	11	16
C	7	20
Pathology		
Alcoholic cirrhosis	18	17
Biliary cirrhosis	5	8
Cryptogenic cirrhosis	8	9
Chronic active hepatitis	5	3
Appearance of staple-line erosion		
At first endoscopy (n)	11	–
Mean(s.e.m.) time (weeks)	53(11·8)	–
Range (weeks)	0·5–212	–
Sclerotherapy		
Total	22	23
Before transection	12	14
After transection	10	9
Symptoms of reflux	12	5
Portal systemic shunt	1	0
Staple protrusion	1	0

The presence of staple-line erosion was usually associated with rebleeding, but could be identified in seven patients without recurrent bleeding and may represent a potential source of bleeding in such patients.

The lower mean blood transfusion requirements support the view that rebleeding from staple-line erosion is usually minor. The frequency of rebleeding from this lesion, however, coupled with the concern that any episode of rebleeding might be variceal, may lead to recurrent hospital admissions.

The finding that equal numbers of patients with and without staple-line erosion had received sclerotherapy suggests that mucosal injury is an unlikely cause. Staple protrusion does not seem to predispose to the development of this lesion. The persistence of portal hypertension seems an unlikely contributory factor as the single patient with bleeding from staple-line erosion who underwent portosystemic shunting continued to bleed.

As in oesophagitis, where symptoms of oesophageal reflux do not necessarily predict the presence or severity of oesophagitis[18,19], symptoms of reflux do not appear to be associated with the development of staple-line erosion.

Severity of underlying liver disease, assessed by Pugh's grade, cannot predict staple-line erosion. Staple-line erosion can develop only in survivors of stapled oesophageal transection, and survival following surgery for bleeding oesophageal varices is biased in favour of those with less severe liver disease. This explains the greater proportion of patients with Pugh's grade A among those with staple-line erosion.

The pathogenesis of staple-line erosion is unknown, but stapled oesophageal transection is associated with acid reflux defined in manometric studies[20] and by oesophageal pH monitoring[21]. Endoscopic features of acid reflux have been described in patients after transection[17]. The use of acid suppression therapy would therefore seem logical to allow healing of staple-line erosion and prevent rebleeding. Similar management of chronic oesophageal ulceration following injection sclerotherapy has been described[22] and this treatment has been effective in patients with staple-line erosion in a preliminary study[23].

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References

1. Van-Kemmel M. Resection–anastomose de l'oesophage sur-cardial pour rupture de varices oesophagiennes. *Nouv Presse Med* 1976; **5**: 1123–4.
2. Johnston GW. Six years experience of oesophageal transection for oesophageal varices, using circular stapling gun. *Gut* 1982; **23**: 770–3.
3. Hoffman J. Staple transection of the oesophagus for bleeding oesophageal varices. *Scand J Gastroenterol* 1984; **18**: 707–11.
4. Wexler MJ, Stein BL. Non-shunting operations for variceal haemorrhage. *Surg Clin North Am* 1990; **70**: 425–48.
5. Jenkins SA, Shields R. Varices haemorrhage after failed injection sclerotherapy: the role of emergency oesophageal transection. *Br J Surg* 1989; **76**: 49–51.
6. Burroughs AK, Hamilton G, Phillips A, Mezzanote G, McIntyre N, Hobbs KEF. A comparison of sclerotherapy with staple transection of the oesophagus for emergency control of bleeding from oesophageal varices. *N Engl J Med* 1989; **321**: 857–62.
7. Cello JP, Crass R, Trunkey DD. Endoscopic sclerotherapy *versus* oesophageal transection in Child's class C patients with variceal haemorrhage. Comparison with results of porta caval shunt: preliminary report. *Surgery* 1982; **91**: 333–8.
8. Huizinga WJ, Angorn IB, Baker LW. Oesophageal transection *versus* injection sclerotherapy in the management of bleeding oesophageal varices in patients at high risk. *Surg Gynecol Obstet* 1985; **160**: 539–46.
9. Teres J, Baroni R, Bordas JM, Visa J, Pera C, Rodes J. Randomised trial of porta caval shunt, stapling transection and endoscopic sclerotherapy in uncontrolled variceal bleeding. *J Hepatol* 1987; **4**: 159–67.
10. McCormick PA, Greenslade L, Cardin F, Hobbs KEF, McIntyre N, Burroughs AKB. Oesophageal staple transection (OST) as a salvage procedure following failure of acute injection sclerotherapy. *Gut* 1990; **31**: A1214.
11. Spence RAJ, Johnston GW. Results in 100 consecutive patients with stapled oesophageal transection for varices. *Surg Gynecol Obstet* 1985; **160**: 323–9.
12. Wannamaker SR, Cooperman M, Carey LC. Use of the EEA stapling instrument for control of bleeding oesophageal varices. *Surgery* 1983; **94**: 620–6.
13. Koyanagi N, Iso Y, Higashi H, Kitano S, Sugimachi K. Recurrence of varices after oesophageal transection: intra-operative and postoperative assessment by endoscopy. *Br J Surg* 1988; **75**: 9–11.
14. Osborne DR, Hobbs KEF. The acute treatment of haemorrhage from oesophageal varices: a comparison of oesophageal transection and staple gun anastomosis with mesocaval shunt. *Br J Surg* 1981; **68**: 734–7.
15. Pugh RNH, Murray-Lyon IM, Dawson J, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; **60**: 646–9.
16. Hosking SW, Johnson AG. What happens to esophageal varices after transection and devascularisation? *Surgery* 1987; **101**: 531–4.
17. Purri P, Fimmano A, Della Volpe N. Endoscopic follow up of patients with varices operated upon with the use of an EEA stapler. *Panminerva Med* 1984; **26**: 163–4.
18. Petersen H, Johannessen T, Kleveland PM, Fjosne U, Dybdahl JH, Waldum HL. Do we listen to the patient? The predictive value of symptoms. *Scand J Gastroenterol* 1988; **23**(Suppl 155): 30–6.
19. Heading RC. Epidemiology of oesophageal reflux disease. *Scand J Gastroenterol* 1989; **24**(Suppl 168): 33–7.
20. Spence RAJ, Johnston GW, Parks TG. Oesophageal manometry in patients with varices and following oesophageal transection. *Br J Surg* 1985; **72**: 96–8.
21. Spence RAJ, Johnston GW, Parks TG. Prolonged ambulatory pH monitoring in patients following oesophageal transection and control subjects. *Br J Surg* 1985; **72**: 99–101.
22. Gimson A, Polson R, Westaby D, Williams R. Omeprazole in the management of intractable oesophageal ulceration following injection sclerotherapy. *Gastroenterology* 1990; **99**: 1829–31.
23. Kaye GL, Siringo S, Mistry P, McCormick PA, Hobbs KEF, Burroughs AK. Omeprazole in the management of staple line erosion of the oesophagus following transection for variceal bleeding. *Gut* 1989; **30**: 745 (Abstract).

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Perioperative blood transfusion does not promote recurrence and death after mastectomy for breast cancer

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Several reports suggest that perioperative blood transfusion promotes recurrence and death after cancer surgery. We studied the effect of transfusion in 1599 patients who had mastectomy for carcinoma of the breast. In 228 transfused patients the disease recurred in 110 (48 per cent), compared with 647 (47 per cent) of 1371 non-transfused patients (P = *0·85). The 5-year recurrence-free survival rate was 0·54 in the transfused patients and 0·60 in the non-transfused group* (P = *0·44). The transfused patients had a higher prevalence of risk factors than the non-transfused patients. Cox's multiple regression analysis confirmed that perioperative blood transfusion was of no importance. The study does not support the hypothesis that perioperative blood transfusion promotes recurrence after operation for breast cancer.*

In recent years several papers have suggested a detrimental effect of perioperative blood transfusion on recurrence and death after cancer surgery[1,2]. The issue has been most extensively studied in patients with colorectal cancer[3], but a detrimental effect has also been reported for other cancers, among them breast cancer[4]. Other workers have been unable to confirm these findings[5–7], or have been able to demonstrate it only in subgroups defined during the data analysis[8].

In 1977 the Danish Breast Cancer Cooperative Group (DBCG) started a nationwide study of patients operated on for invasive breast cancer[9]. The database of the DBCG study contains standardized prospectively collected data including accurate follow-up data on more than 20000 patients[10]. The aim of the present paper is to use these data to test the hypothesis that perioperative blood transfusion increases the recurrence rate and death rate after mastectomy for carcinoma of the breast.

Patients and methods

DBCG studies

The DBCG was established in 1976 with the purpose of standardizing and evaluating the treatment of breast cancer. Most Danish hospitals participate in the study, and approximately 2000 patients are entered into it each year[9,10].

Surgical procedure. During the first 5-year period of the study (1977–1982, DBCG 77 protocols) all patients had a modified total mastectomy with partial dissection of the axillary lymph nodes as described by Cady[11].

Other procedures. Histopathological examination, randomization to adjuvant therapy and follow-up examinations were standardized and have been described in detail elsewhere[9,10]. Anaplasia was given a numerical score as previously described[12].

Adjuvant treatment. In the DBCG 77 protocols low-risk patients (i.e. patients with small tumours, without fixation to skin or deep fascia and with no axillary lymph node metastasis) were allocated to observation only. Premenopausal and postmenopausal high-risk patients were allocated to adjuvant radiotherapy and/or chemotherapy. The criteria for protocol allocation and the type and dose of adjuvant treatment have recently been reviewed in detail[10].

Exclusion criteria. Patients with previous malignant disease, distant metastasis or medical contraindication, and patients not operated on according to the DBCG surgical guidelines, were not entered into the DBCG protocol.

Transfusion. DBCG protocols do not consider indications for blood transfusion, which was given at the discretion of the surgeon or the anaesthetist.

Present study

Patients. The study considered only patients operated on in hospitals in the central or suburban Copenhagen area (Copenhagen or Frederiksberg Municipalities or Copenhagen County) and entered into the DBCG 77 protocols. These criteria were fulfilled by 1869 patients. From the DBCG database we extracted clinical, surgical and histopathological data, as well as information on treatment protocol and treatment regimen and follow-up data. Information on 39 patients (2 per cent) operated on in two hospitals entering fewer than five patients a year was excluded. Of the remaining 1830 patients operated on in 11 hospitals, the original hospital records were incomplete or could not be retrieved in 231 (12 per cent). Thus, 1599 patients (86 per cent) were eligible for analysis.

Methods. As DBCG does not record transfusion data, the original hospital records were reviewed. According to Danish hospital practice, the number and type of blood products transfused are carefully recorded on a special transfusion record in the hospital case notes. The number and type of transfusions given within 30 days before or after the day of operation were related to the DBCG data.

Statistical methods. Groups of data were summarized by median, minimum and maximum values. Standard non-parametric tests were used. In the life-table analyses we determined recurrence-free survival, time being measured from the day of operation to the day of objective demonstration of recurrence. We also analysed overall survival (time from the day of operation to the day of death from any cause) and breast cancer specific survival (time from the day of operation to the day of death, where breast cancer was stated as the primary cause of death). The unadjusted survival rates were calculated by the Kaplan–Meier technique and were compared by the log rank test[13]. Multiple regression by the Cox model was used to adjust for differences in prognostic variables[14]. To facilitate the Cox analysis, we introduced a new variable, 'risk factors', which was considered to be positive if one or more of the well known risk factors (tumour size >50 mm, adhesion to skin, invasion into deep fascia, axillary lymph node metastasis) were present. The unadjusted and recurrence-free survival rates varied between the 11 departments studied. However, recurrence-free survival did not differ between transfused and non-transfused patients in nine departments. In two departments, transfused patients had significantly worse survival. A Type I error risk of 0·05 for the rejection of the null hypothesis was chosen.

Results

Of 1599 patients studied, 228 patients (14 per cent) had

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undergone transfusion. The number of transfusions according to type of blood product are shown in *Table 1*. More than half of the transfused patients received 1 unit only, and only 6 per cent received more than 2 units. Of the 367 units, 317 (86 per cent) were whole blood and only 3 per cent of the units transfused were plasma-poor products. Between the 11 departments, the frequency of transfusion varied considerably from 0 to 28 per cent ($P<0{\cdot}0001$).

The patients receiving transfusion had larger tumours than the non-transfused patients (*Table 2*). Although statistically significant, the slightly greater age of the transfused patients was not clinically relevant. The transfused patients had a higher prevalence of deep fascia invasion, and a higher number of tumour-positive lymph nodes (*Table 3*). However, the distribution of histological diagnoses and the scoring for cellular anaplasia were equal in the two groups. The tendency for more advanced disease in the transfused patients is reflected in the proportion of patients who received adjuvant treatment: 61 per cent of the transfused patients compared with 48 per cent of the non-transfused patients ($P=0{\cdot}02$).

Table 1 *Type and number of transfusions given in 228 patients*

	No. of units					
	1	2	3	4	5	>5
Whole blood	110	78	4	4	1	1*
Packed blood	11	8	0	0	0	0
Washed erythrocytes	4	7	0	0	0	0
Plasma	1	1	0	0	0	0
Plasma concentrate	2	0	0	0	0	0
Total no. of units transfused irrespective of type	125	90	5	6	1	1*

*One patient received 18 units

Table 2 *Clinical data related to blood transfusion in 1599 patients operated on for breast cancer*

	Non-transfused ($n=1371$)	Transfused ($n=228$)	*P*
Age (years)*	58·4 (26–89)	58·6 (22–86)	<0·0001‡
Postmenopausal	875 (64%)	143 (63%)	0·73§
Tumour size (mm)*	35·0 (0–150)	42 (0–180)	<0·0001‡
Localization†			
Lateral	869 (66%)	133 (61%)	
Medial	346 (26%)	63 (29%)	0·38§
Central	103 (8%)	21 (10%)	

*Values are median (range); †data missing for some patients; ‡Mann–Whitney *U* test; §χ^2 test

Table 3 *Histopathological data related to blood transfusion in 1599 patients operated on for breast cancer*

	Non-transfused ($n=1371$)	Transfused ($n=228$)	*P*
Tumour size (mm)*	32 (0–150)	36 (0–120)	<0·0001†
Fixation to skin	94 (6·9%)	19 (8·3%)	0·26‡
Invasion of muscle	181 (13·2%)	49 (21·5%)	0·002‡
Number of axillary lymph nodes removed*	4 (0–22)	4 (0–17)	0·11†
No. of tumour-positive axillary lymph glands*	0 (0–19)	1 (0–12)	0·006†
Histological diagnosis			
Infiltrative cancer	1138 (83·0%)	197 (86·4%)	
Medullary cancer	21 (1·5%)	5 (2·2%)	
Papillary cancer	7 (0·5%)	1 (0·4%)	
Cribriform cancer	9 (0·7%)	1 (0·4%)	
Mucous cancer	40 (2·9%)	5 (2·2%)	0·95‡
Lobular cancer	51 (3·7%)	6 (2·6%)	
Squamous cell cancer	4 (0·3%)	1 (0·4%)	
Paget's disease	5 (0·4%)	1 (0·4%)	
Other type	62 (4·5%)	8 (3·5%)	
Unknown	34 (2·5%)	3 (1·3%)	
Anaplasia score*	6 (2–9)	6 (3–9)	0·88†

*Values are median (range); †Mann–Whitney *U* test; ‡χ^2 test

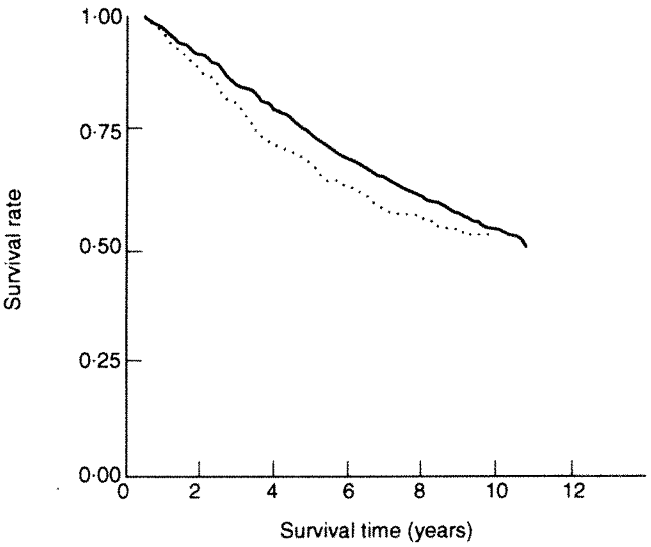

Figure 1 *Unadjusted recurrence-free survival plot in 1599 patients operated on for breast cancer. In 228 patients who had perioperative blood transfusion the 5-year survival rate was 0·54* versus *0·60 in 1371 non-transfused patients* (P*=0·44, log rank test). ——, Non-transfused; -----, transfused*

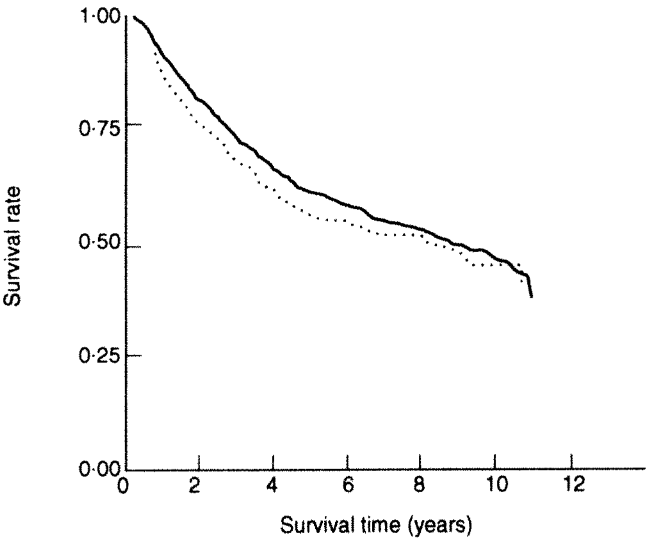

Figure 2 *Unadjusted overall survival plot in 1599 patients operated on for breast cancer. In 228 patients who had perioperative blood transfusion the 5-year survival rate was 0·67,* versus *0·73 in 1371 non-transfused patients* (P *= 0·24, log rank test). ——, Non-transfused; -----, transfused*

At the latest follow-up in autumn 1988 (between 6 and 11 years after the operation) 110 (48 per cent) of the transfused patients had had a recurrence *versus* 647 (47 per cent) of the non-transfused patients ($P=0{\cdot}85$). In both groups one-third of the recurrences were local and two-thirds were distant metastases. About half of the patients had died; breast cancer was stated as the primary cause of death in 75 per cent with no detectable difference between the groups. The unadjusted recurrence-free survival rates showed a minor but not statistically significant advantage for the non-transfused patients (*Figure 1*). The 5-year rates were 0·60 and 0·54 ($P=0{\cdot}44$, log rank test). Similarly, the non-transfused patients had slightly better unadjusted overall survival (*Figure 2*) and unadjusted breast cancer specific survival (*Figure 3*) than the transfused patients (*Figure 2*), but there was no statistically confirmed improvement in 5-year survival.

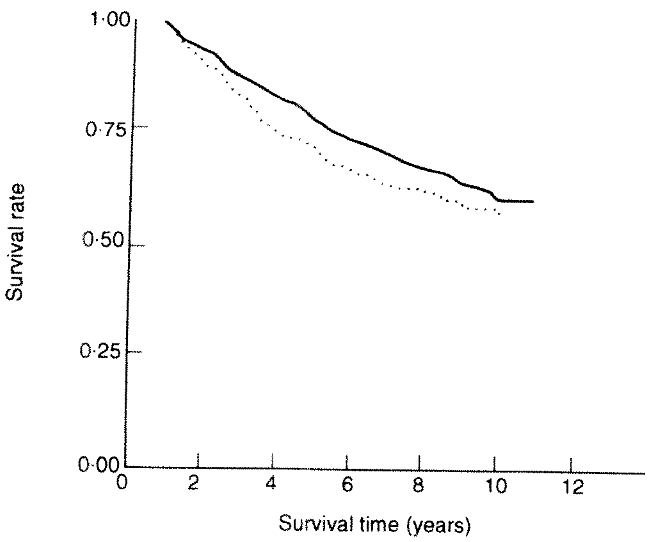

Figure 3 *Unadjusted breast cancer specific survival plot in 1599 patients operated on for breast cancer. In 228 patients who had perioperative blood transfusion the 5-year survival rate was 0·69, versus 0·76 in 1371 non-transfused patients* (P = *0·12, log rank test*). ——, *Non-transfused;* -----, *transfused*

Table 4 *Result of Cox's multiple regression analysis of breast cancer recurrence-free survival*

	Score	Regression coefficient	s.d.	χ^2	*P*
Primary model					
Age		0·134	0·096	1·93	0·16
≤60 years	0				
>60 years	1				
Menopausal state		0·376	0·105	12·9	<0·0001
Premenopausal	0				
Postmenopausal	1				
Risk factor*		0·466	0·007	39·5	<0·0001
Absent	0				
Present	1				
Anaplasia score		0·485	0·075	41·5	<0·0001
Points <6	0				
Points ≥6	1				
Transfusion		0·015	0·104	0·02	0·89
No. of units = 0	0				
No. of units > 0	1				
Final model					
Menopausal state		0·469	0·079	34·9	<0·0001
Premenopausal	0				
Postmenopausal	1				
Risk factor*		0·470	0·074	40·4	<0·0001
Absent	0				
Present	1				
Anaplasia score		0·485	0·075	41·5	<0·0001
Points <6	0				
Points ≥6	1				

* Tumour size >50 mm, adhesion to skin, invasion into deep fascia or axillary lymph node metastasis at the time of operation

Calculation of unadjusted recurrence-free and survival rates in various subgroups confirmed the significance of the classical risk factors, such as tumour size, adhesion to skin, invasion into deep fascia and axillary lymph node metastasis. The grade of anaplasia and menopausal state significantly affected all survival parameters, and age was an important determinant of overall survival, but not of recurrence-free or breast cancer specific survival.

The primary Cox regression model for recurrence-free survival included age, menopausal state, anaplasia score, risk factors and transfusion (*Table 4*). Age and transfusion were insignificant, but menopausal state, anaplasia score and risk factor were highly significant. The final model included menopausal state, anaplasia score and risk factor and was highly significant ($P < 0.0001$). Using the figures from the primary model, the odds ratio for an increased incidence of breast cancer recurrence in the transfused patients was 1·01 (95 per cent confidence limits 0·81–1·25).

For overall survival and breast cancer specific survival the primary Cox models included age, menopausal state, risk factor, anaplasia score and transfusion. Again, transfusion was of no importance and the final model included menopausal state, risk factor, anaplasia and (for overall survival) age.

Discussion

The present study does not support the hypothesis that perioperative blood transfusion promotes recurrence and death after mastectomy. Although transfused patients had a slightly poorer survival rate than non-transfused patients, this was not significant. The transfused patients also had a higher prevalence of well established and suspected risk factors. When the effects of these risk factors were eliminated by the Cox regression analysis, there was no effect of blood transfusion on recurrence and death rates.

Studies which have failed to demonstrate an adverse effect of blood transfusion on recurrence and survival have been criticized on a number of points. From a methodological point of view, the retrospective acquisition of data with resulting bias and inaccuracy, or the application of insufficient statistical methods or insufficient sample size, may mask a real effect and result in a Type 2 statistical error. However, these objections seem less relevant to the present study. Clinical and histopathological data were evaluated in a standardized manner and prospectively collected, and complete long-term follow-up data were available. The only information not collected prospectively were the transfusion data, but these are carefully collected in Danish hospital records. Despite the size of the present study, no effect of transfusion was seen, although the 95 per cent confidence limits for the odds ratio for increased risk of recurrence after transfusion range from 0·81 to 1·25, which could include effects of clinical importance. However, this figure should be compared with the effect of the classical risk factors, which is 1·59 (95 per cent confidence limits 1·37–1·84).

A more specific criticism has been raised by Blumberg *et al.*[15]. They claimed that the detrimental effect of blood transfusion is due to a plasma factor. Consequently, transfusion of plasma-poor products could have masked a real effect in studies without a demonstrable effect of transfusion. In the present study only 11 patients received plasma-poor products alone. Thus the negative result cannot be ascribed to transfusion of plasma-poor products.

Nowak and Ponsky[8] studied 81 patients operated on for breast cancer. In a retrospectively defined subgroup of 50 patients receiving tamoxifen, they found that the transfused patients had a worse prognosis than those not transfused. In the present study 212 patients received tamoxifen, and even in this subgroup the survival rates were identical in the transfused and non-transfused groups. We did not include treatment with any form of adjuvant therapy in the Cox regression analysis for two reasons. First, it is probably unjustified to do so because the administration of adjuvant therapy occurred after the decision to transfuse or not, and so may not have been an independent variable. Secondly, almost all patients with risk factors received adjuvant therapy, so analysis of these patients would require a very complex model.

The fundamental point at issue is whether the association between blood transfusion and the various adverse effects is a causal one or whether transfusion and the adverse effect merely have a common underlying cause. Cox's regression analysis is a powerful tool for evaluating the relative influence of various well defined and accurately recorded background variables on survival parameters. However, it cannot handle ill-defined or unrecorded variables, like tumour aggressiveness or technically difficult surgery. We suspect that these factors could be the common underlying causes for the adverse effects of blood transfusion reported in other studies.

The issue of whether blood transfusion can influence recurrence rates of breast cancer could only be solved in a randomized, prospective study. With the well established risk of blood transfusion, for instance transmission of HIV, such a study would be very difficult to conduct. The negative result of the present study indicates that breast cancer will not be a fruitful area into which to launch such a study. Indeed, it could be argued that in this series of 1599 patients only one patient (the patient who received 18 units) was in indisputable need of blood transfusion. We conclude that blood transfusion is rarely necessary in the surgical management of breast cancer, and that, when indicated, no deleterious effect on recurrence or survival can be demonstrated.

Acknowledgements

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References

1. Burrows L, Tartter P. Effect of blood transfusion on colonic malignancy recurrence rate. *Lancet* 1982; **ii**: 662 (Letter).
2. Burrows L, Tartter P, Aufses A. Increased recurrence rates in perioperatively transfused colo-rectal malignancy patients. *Cancer Detect Prev* 1987; **10**: 361–9.
3. Taylor RMR, Parrott NR. Red alert. *Br J Surg* 1988; **75**: 1049–50.
4. Tartter PI, Burrows L, Papatestas AE *et al.* Perioperative blood transfusion has prognostic significance for breast cancer. *Surgery* 1985; **97**: 225–9.
5. Foster RS, Foster JC, Constanza MC. Blood transfusion and survival after surgery for breast cancer. *Arch Surg* 1984; **119**: 1138–40.
6. Voogt PJ, Cornelis JH, Brand A *et al.* Perioperative blood transfusion and cancer prognosis: different effects of blood transfusion on prognosis of colon and breast cancer patients. *Cancer* 1987; **59**: 836–43.
7. Eickhoff JH, Andersen PM, Nørgård H. Effect of perioperative blood transfusion on recurrence and death after mastectomy for breast cancer. *Acta Chir Scand* 1988; **154**: 425–8.
8. Nowak MM, Ponsky JL. Blood transfusion and disease-free survival in carcinoma of the breast. *J Surg Oncol* 1984; **27**: 124–30.
9. Andersen KW, Mouridsen HT, Castberg T *et al.* Organisation of the Danish Adjuvant Trials in Breast Cancer. *Dan Med Bull* 1981; **28**: 102–12.
10. Andersen KW, Mouridsen HT. Danish Breast Cancer Cooperative Group (DBCG): a description of the register of the nation-wide programme for primary cancer. *Acta Oncol* 1988; **27**: 627–47.
11. Cady B. Total mastectomy and partial axillary dissection. *Surg Clin North Am* 1973; **53**: 313–18.
12. Andersen JA, Fischermann K, Hou-Jensen K *et al.* Selection of high risk groups among prognostically favourable patients with breast cancer: an analysis of the value of prospective grading of tumour anaplasia in 1048 patients. *Ann Surg* 1981; **194**: 1–3.
13. Peto R, Pike MC, Armitage P *et al.* Design and analysis of randomized clinical trials requiring prolonged observation of each patient. *Br J Cancer* 1977; **35**: 1–39.
14. Cox DR. Regression models and life tables. *J R Stat Soc* 1972; **34**: 187–220.
15. Blumberg N, Heal JM, Murphy P *et al.* Association between transfusion of whole blood and recurrence of cancer. *Br Med J* 1986; **293**: 530–3.

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Trauma audit: experience in north-east Scotland

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The management of 125 patients with trauma treated at Aberdeen Royal Infirmary from 1 January 1988 has been analysed using a microcomputer-based hospital trauma registry incorporating trauma and injury severity scores (TRISS) methodology. These patients fulfilled the North American Major Trauma Outcome Study (MTOS) inclusion criteria and were the first for whom data were available. Sixty-six patients had multiple injuries, of whom 52 were suffering from major trauma (defined as an injury severity score of 16 or greater). There were 14 deaths in the series, three (21 per cent) of which were considered to be preventable. Surgery was required in 84 (67·2 per cent) patients, of whom 59 (70 per cent) were operated on by a consultant or senior registrar. Five of six critically injured patients who died from their injuries were operated on by a consultant.

The management of patients suffering from multiple injuries is currently attracting attention[1,2], with claims that trauma care is suboptimal throughout the country. This may result in people dying unnecessarily from treatable conditions which are frequently missed[3,4] or from the policy of taking trauma victims to the nearest hospital without regard to the expertise and resources available at that hospital. Comparisons have been made with the situation in the USA before regionalization of trauma services and the establishment of trauma centres[5–8]. In its report on the management of patients with multiple injuries, The Royal College of Surgeons of England has recommended the setting up of American-style trauma centres in the UK[9].

There is a paucity of accurate data with which to judge what is happening in this country. Aberdeen Royal Infirmary is similar to an American-style trauma centre in that it has all the specialties required in a level one trauma centre on site[10]. It receives virtually all the major trauma patients from the Grampian region. This paper evaluates the current level and outcome of trauma care delivered in this region.

Patients and methods

Aberdeen Royal Infirmary serves a mixed urban and rural population of approximately 500 000 people. The accident and emergency department treats 50 000 new patients a year, of whom approximately 80 per cent have trauma-related injuries. Computed tomography and magnetic resonance imaging facilities are available.

From 1 January 1988 data were collected prospectively on 125 eligible trauma patients and stored in a computerized trauma registry program written for this purpose. The criteria for inclusion in the registry were the same as those used in the Major Trauma Outcome Study (MTOS) in the USA and are listed in *Table 1*. The program runs on IBM-compatible computers and uses a relational database system (dBASE IV, Ashton–Tate Ltd., Birmingham, UK) to store, retrieve and analyse data.

Anatomical injuries diagnosed by examination, radiographs, scans, surgery or autopsy were scored according to severity using the 1985 revision of the abbreviated injury scale (AIS)[11] in which the body is divided into six regions and each injury is rated from 1 to 6. Minor injury is represented by 1 and 6 represents an injury which is virtually unsurvivable. The injury severity score[12] was then calculated by adding the squares of the highest AIS values in each of the three most severely injured body regions. The revised trauma score[13] was calculated using the Glasgow coma scale, systolic blood pressure and respiratory rate. These values were then used to calculate the survival probability by the trauma and injury severity scores (TRISS) method, based on a study of normative outcomes in a database of more than 100 000 patients in the USA[14]. Survival probability values range from 0 to 1·0.

Unexpected deaths were those occurring in patients whose survival probability was greater than 0·5 and unexpected survivors were patients with a probability of survival of less than 0·5 who lived. Major trauma was defined as an injury severity score of 16 or more.

The *Z* statistic described by Flora[15] allows comparison of deaths or survivors between two patient subsets. In the present study the *Z* value was used to compare the observed number of deaths with the predicted number based on the MTOS population. For the *Z* value to be valid there must be a good correlation in injury severity mix between the two patient groups as measured by the heuristic *M* statistic[14]. *M* values of less than 0·88 indicate an injury severity mismatch, and an unreliable *Z* value.

Results

There were 85 male patients, with a group mean age of 41·5 years (range 14–93). The distribution of patients and outcome according to the severity of injury is shown in *Figures 1–3*. Sixty-six patients had multiple injuries, 52 with major trauma, and 14 died.

The aetiology of injury is listed in *Table 2*. Blunt trauma occurred in 122 patients and penetrating trauma in only three patients. *Table 3* shows the distribution of admission by time of day and day of the week. More than half of the patients arrived out of 'office hours'. Of the patients attending at the weekend, 73 per cent presented between 16.00 hours and 08.00 hours.

The disposal of patients from the accident and emergency department is shown in *Table 4*. The overall mortality rate was 11·2 per cent; 4·8 per cent died in the accident and emergency department. The *Z* value in this study was 1·01, indicating a slight excess in the observed number of deaths compared with the expected number (not statistically significant ($P > 0.05$)). The correlation in injury severity mix between these patients and the North American MTOS population was excellent ($M = 0.99$). Despite 52·8 per cent of patients suffering multiple injuries, only one (0·8 per cent) went directly to the intensive care unit and overall only five (4·0 per cent) received intensive care. The mean time spent in intensive care was 8·8 days (range 1–25 days).

The mean time spent in the accident and emergency department is shown in *Table 5*. Sixteen patients spent more

Table 1 *Hospital Trauma Registry inclusion criteria*

1. All trauma deaths including dead on arrival
2. All patients admitted for 72 h or more due to injury
3. All inter-hospital transfers for treatment of acute injury
4. All injured patients treated in intensive care (patient:nurse ratio 2:1)

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than 4 h in the department and ten had major trauma, of which one subsequently died. Of the patients who received intravenous fluids, those who died received approximately 1 litre more colloid and 400 ml more crystalloid than those who survived with major injuries, reflecting greater severity of injury (*Table 6*). Despite early venous access, 23 per cent of patients with major injuries received no intravenous fluids while in the department.

Most patients suffered a combination of head, chest and skeletal injury, the last occurring in 84 per cent of patients (*Table 7*). The mean time taken for specialists to attend when requested was 23·7 min but there was considerable variation between and within specialties (*Table 8*).

Eighty-four patients (67·2 per cent) underwent emergency surgery. The grade of surgeon performing the operation is shown in *Table 9*. Twenty-six (31 per cent) patients were operated on by a consultant, 33 (39 per cent) by a senior registrar, 21 (25 per cent) by a registrar and only 2 (2 per cent) by a senior house officer. All critically injured patients (except one) who underwent surgery but died from their injuries were operated on by a consultant.

The mean duration of hospital stay was 21·7 days. Patient disposal on discharge is detailed in *Table 10*.

Seven of the 14 deaths were unexpected in that their survival probability was greater than 0·5. Review of these cases revealed three (21 per cent) deaths which were judged preventable (*Table 11*). Unexpected survival occurred in only one patient, a 74-year-old woman with head, face and chest injuries. Her injury severity score and survival probability were 38 and 0·18, respectively. She required ventilation for 24 days in the intensive

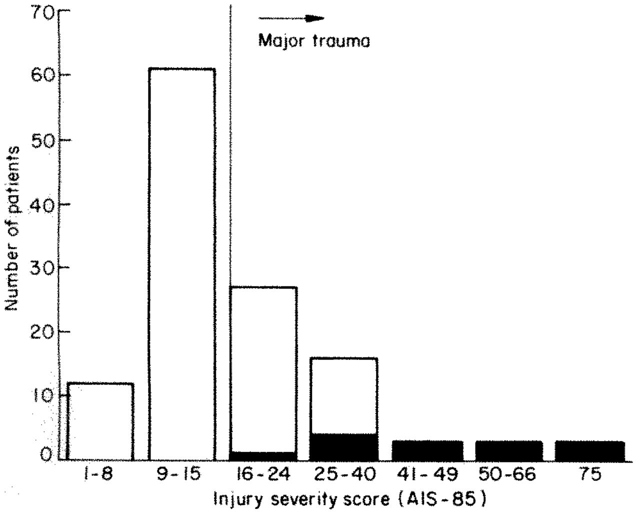

Figure 1 *Distribution of patients according to injury severity.* ■, *Deaths*

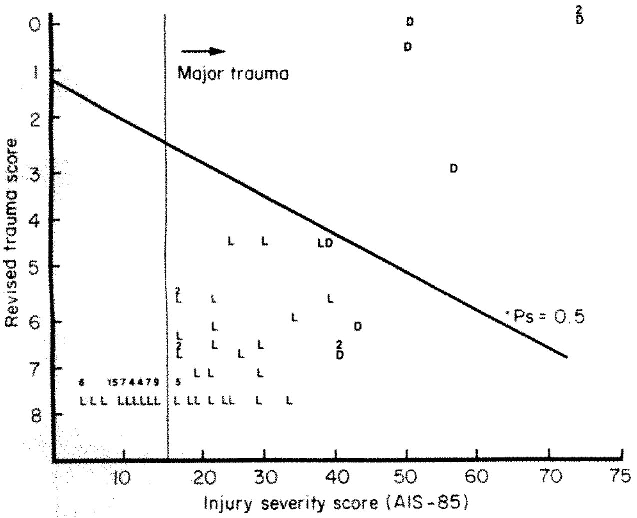

Figure 2 *Outcome according to revised trauma score and injury severity score in 93 patients aged 54 years or less. L, Lived; D, died. Values above L and D are the numbers of patients in each category. * Ps = 0.5, line representing a survival probability of 50 per cent*

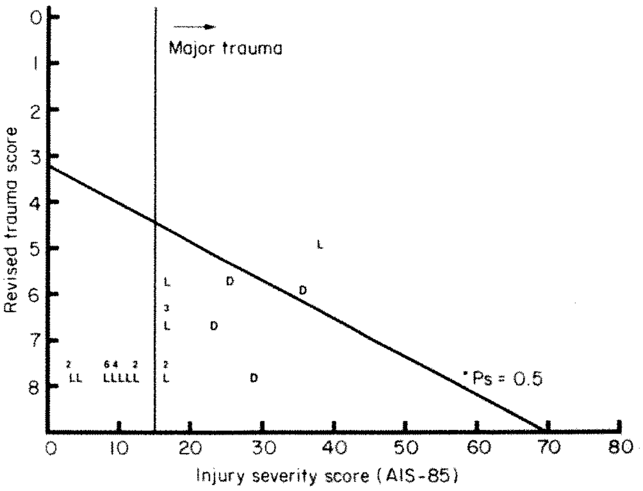

Figure 3 *Outcome according to revised trauma score and injury severity score in 29 patients aged 55 years or more. L, Lived; D, died. Values above L and D are the numbers of patients in each category. * Ps = 0.5, line representing a survival probability of 50 per cent*

Table 2 *Cause of injury in 125 patients*

Aetiology	Number of patients
Road traffic accident	74 (59·2)
Other vehicle accident	8 (6·4)
Fall	29 (23·2)
Other	14 (11·2)
Total	125 (100)

Values in parentheses are percentages

Table 4 *Disposal of patients from the accident and emergency department*

Patient disposal	Number
Admitted to ward	97 (77·6)
Admitted to theatre	21 (16·8)
Admitted to intensive care	1 (0·8)
Died in department	6 (4·8)
Total	125 (100)

Values in parentheses are percentages

Table 3 *Distribution of admissions according to time and day of week*

Admission time	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Total
00.01–08.00	3	1	1	1	1	2	1	10
08.01–16.00	4	12	12	10	11	8	3	60
16.01–24.00	5	12	6	8	6	8	10	55
Total	12	25	19	19	18	18	14	125

Table 5 *Age, severity of injury and length of hospital stay by patient group*

	Number of patients (n = 125)	Mean age (years)	Mean injury severity score	Mean time in accident and emergency (h)	Mean stay in intensive care unit (days)	Mean stay in hospital (days)
Trauma deaths	14	50·1	46·9	2·1	6·0 (n = 1)	2·6
Major trauma survivors	38	37·5	22·5	2·9	9·5 (n = 4)	29·0
Other trauma survivors	73	41·9	10·0	2·5	0·0	21·1

care unit, developed septic shock and renal failure, but made a good recovery and was discharged home.

Table 12 lists factors in patient management identified as avoidable, but which did not affect mortality.

Discussion

This study highlights the importance of extending audit to all patients with trauma, regardless of survival. If only deaths are audited then some unexpected survivors may not be identified and an institution may appear to be performing worse than it actually is.

Of the seven patients whose deaths were unexpected, six had an injury severity score above the median lethal dose of injury. On the basis of injury severity score alone their risk of dying would be 50 per cent or greater[16]. Each unexpected death must be reviewed to identify avoidable factors which may have contributed to that death and a judgement made as to whether or not death was preventable.

The rate of preventable death (21 per cent) is comparable to that quoted by Anderson *et al.*[3] and Gilroy[17] but lower than the 50–70 per cent rate quoted in North American studies[6–8]. All the deaths in the present series occurred in patients who were severely injured and who would be judged by experienced clinicians to have a high risk of mortality. Only one patient had an injury severity score of less than the median lethal dose of injury. This contrasts with the findings of Court-Brown[4],

Table 6 *Fluid resuscitation by patient group*

Patient group	Mean crystalloid infusion (ml)	Mean colloid infusion (ml)
Trauma deaths	1250 (7)	2356 (9)
Major trauma survivors	840 (24)	1468 (14)
Other trauma survivors	703 (38)	950 (14)

Values in parentheses are the numbers of patients in each group

Table 7 *Distribution of injuries in 125 patients*

Injury site	Number	Most severe injury
Head	55 (44·0)	30 (24·0)
Chest	33 (26·4)	15 (12·0)
Abdomen	7 (5·6)	4 (3·2)
Spine	13 (10·4)	10 (8·0)
Limbs/pelvis	105 (84·0)	60 (48·0)
Other	6 (4·8)	6 (4·8)

Values in parentheses are percentages

Table 8 *Response times by specialty*

Specialty	Total referrals	Mean response time (min)	30–60 min	≥60 min
Orthopaedic surgery	83	24·5	6 (7·2)	14 (16·9)
Neurosugery	27	26·1	3 (11·1)	2 (7·4)
General surgery	12	19·2	1 (8·3)	0
Thoracic surgery	10	16·2	0	1 (10·0)
Plastic surgery	7	8·6	0	0
Oral surgery	5	67·0	0	2 (40·0)
Intensive care	4	18·8	0	1 (25·0)
Vascular surgery	3	6·7	0	0
Ophthalmic surgery	2	11·0	0	0
ENT surgery	1	10·0	0	0
Total	154	23·7	10 (6·5)	20 (13·0)

Values in parentheses are percentages

Table 9 *Grade of surgeon performing emergency surgery*

Patient group	Consultant	Senior registrar	Registrar	Senior house officer	Not known
Trauma deaths					
Number	5	0	1	0	0
Mean ISS	48·2	0	41·0	0	0
Duration of operation (min)	80·0	0	135·0	0	0
Mean blood units	15·8	0	9·0	0	0
Major trauma survivors					
Number	11	11	4	0	0
Mean ISS	24·7	20·0	22·5	0	0
Duration of operation (min)	120·5	118·6	60·0	0	0
Mean blood units	8·0	6·7	2·0	0	0
Other trauma survivors					
Number	10	22	16·0	2	2
Mean ISS	10·3	10·7	10·3	10·0	8·0
Duration of operation (min)	98·5	100·5	71·9	47·5	107·5
Mean blood units	3·8	3·6	2·8	4·0	2·0

ISS, injury severity score

who reported that the mean injury severity score of road traffic accident victims dying after admission to a major teaching hospital was 25, and 69·6 per cent were below the median lethal dose of injury. Similarly, the mean injury severity score of deaths from blunt trauma in Northern Ireland was 28·1[17]. In Ontario, Wright *et al.*[18] found that 53 per cent of patients who were not treated in a trauma centre and who died were below the median lethal dose of injury, compared with only 5·8 per cent of patients treated in a trauma centre.

The mortality rate in the accident and emergency department of Aberdeen Royal Infirmary was 4·8 per cent, which compares favourably with the 9 per cent quoted in the Working Party report[9]. The small number of admissions to the intensive care unit may highlight problems regarding the availability of beds and admission policies. Spence *et al.*[19] found unexpected survivors in patients who were treated for a prolonged period in intensive care, as was the only unexpected survivor in this study.

The factors involved in preventable deaths were mainly delayed or inadequate treatment, as noted in other studies[4,18,20,21]. None of the preventable deaths in this study was due to easily remediable surgical lesions which were missed. Some patients who died had operable lesions but the consultant decided that surgery was not indicated or appropriate on clinical grounds, which is a valid decision in some cases.

The long periods of time spent by some patients in the accident and emergency department is a cause for concern. It is partly attributable to the time required to assess and resuscitate the patient properly. Waiting for other specialists to arrive and for operating theatre time are other important avoidable factors.

A surprising finding was that 23 per cent of patients with major injuries received no intravenous fluids while in the department. These patients were generally suffering from class II haemorrhage (15–30 per cent blood loss). The clinical signs of shock are quite subtle in this group and the need for early fluid replacement is not always appreciated by junior medical staff.

In conclusion, avoidable factors have been identified which may have contributed to the death of 21 per cent of the patients who died, and these deaths have therefore been regarded as preventable. Study of all victims of major trauma identifies deficiencies which may contribute to morbidity as well as mortality.

Table 10 *Patient disposal on discharge*

Disposal	Number
Home (no support)	88 (70·4)
Home (professional support)	4 (3·2)
Transfer to other hospital	6 (4·8)
Convalescent care	4 (3·2)
Rehabilitative care	3 (2·4)
Long-term care	6 (4·8)
Died	14 (11·2)
Total	125 (100)

Values in parentheses are percentages

Table 12 *Avoidable factors in patient management*

Factor	Number occurring
Unintentional delay in operation	10
Unplanned return to theatre	4
Transfer to intensive care unit	2
Missed diagnosis	11

Table 11 *Preventable trauma deaths*

Case	Age (years)	Injuries	Injury severity score	Survival probability	Avoidable factors
1	77	Open fracture tibia/fibula, subarachnoid haemorrhage	22	0·85	Delay in operation
2	50	Flail chest, severe head injury, splenic rupture, liver lacerations	41	0·90	Unprotected airway, delayed/ inadequate treatment
3	80	Fracture C5, T5/T6, disrupted discs C2–C5, multiple rib fractures, mediastinal haemorrhage, bilateral small haemothoraces	29	0·82	Error in diagnosis, severity of injuries not appreciated, inadequate fluid replacement

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References

1. Yates DW. Action for accident victims. *Br Med J* 1988; **297**: 1419–20.
2. Trunkey DD. A time for decisions. *Br J Surg* 1988; **75**: 937–9.
3. Anderson ID, Woodford M, de Dombal FT, Irving M. Retrospective study of 1000 deaths from injury in England and Wales. *Br Med J* 1988; **296**: 1305–8.
4. Court-Brown CM. Care of accident victims. *Br Med J* 1989; **298**: 115–16 (Letter).
5. Heyworth J, Yates DW. Management of the severely injured patient. *Surgery* 1989; **57**: 1351–9.
6. West JG, Trunkey DD, Lim RC. Systems of trauma care. A study of two counties. *Arch Surg* 1979; **114**: 455–60.
7. West JG, Cales RH, Gazzaniga AB. Impact of regionalization – the Orange County experience. *Arch Surg* 1983; **118**: 740–4.
8. Cales RH, Trunkey DD. Preventable trauma deaths – a review of trauma care systems development. *JAMA* 1985; **254**: 1059–63.
9. Commission on the Provision of Surgical Services. *Report of the Working Party on the Management of Patients with Major Injuries.* London: Royal College of Surgeons of England, 1988.
10. Committee on Trauma, American College of Surgeons. Hospital resources for optimal care of the injured patient. *Bull Am Coll Surg* 1979; **64**: 43–8.
11. American Association for Automotive Medicine. *The Abbreviated Injury Scale: 1985 edition.* Des Plaines, Illinois.
12. Baker SP, O'Neill B, Haddon W Jr, Long WB. The Injury Severity Score: a method for describing patients with multiple injuries and evaluating emergency care. *J Trauma* 1974; **14**(3): 187–96.
13. Champion HW, Sacco WJ, Copes WS, Gann DS, Gennarelli TA, Flanagen ME. A revision of the trauma score. *J Trauma* 1989; **29**(5): 623–9.
14. Boyd CR, Tolson MA, Copes WS. Evaluating trauma care: the TRISS method. *J Trauma* 1987; **27**(4): 370–8.
15. Flora JD. A method for comparing survival of burn patients to a standard survival curve. *J Trauma* 1978; **18**: 701–5.

16. Bull JP. Measures of severity of injury. *Injury* 1975; **9**: 184–7.
17. Gilroy D. Deaths from blunt trauma: a review of 105 cases. *Injury* 1984; **15**: 304–8.
18. Wright CS, McMurtry MD, Pickard J. A postmortem review of trauma mortalities – a comparative study. *J Trauma* 1984; **24**(1): 67–8.
19. Spence MT, Redmond AD, Edwards JD. Trauma audit – the use of TRISS. *Health Trends* 1988; **20**: 94–7.
20. Dearden CH, Rutherford WH. The resuscitation of the severely injured in the accident and emergency department – a medical audit. *Injury* 1985; **16**: 249–52.
21. Gordon MWG, Luke C, Robertson CE, Busuttil A. An audit of trauma deaths occurring in the accident and emergency department. *Arch Emerg Med* 1989; **6**: 107–15.

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Short note

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Hepatic artery reconstruction after resection of the hepatoduodenal ligament

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Carcinoma of the gallbladder and bile duct is characterized by early infiltration into the hepatoduodenal ligament along the lymph vessels and nerve sheaths[1,2]. Hence, it may be desirable to treat such tumours by *en bloc* hepatoduodenal ligament resection (HDLR) with removal of the artery and portal vein in the hepatoduodenal ligament. We have performed HDLR for treatment of cancers in the hepatopancreatic region since 1985. Initially, the need for hepatic artery reconstruction was not clear and this procedure was not always carried out. However, anastomotic leakage invariably occurred in patients without hepatic artery reconstruction, suggesting the importance of the arterial supply to the bile duct. To investigate this, the residual blood flow in the common bile duct vessels was measured with a laser Doppler microflowmeter before and after occlusion of the portal vein, hepatic artery and lower part of the common bile duct.

Patients and methods

Fourteen patients who underwent HDLR before December 1989 were studied; 11 had cholangiocarcinoma, two had gallbladder carcinoma, and one had pancreatic carcinoma. Thirty-seven patients with cholangiocarcinoma underwent bile duct reconstruction without hepatic artery resection between 1985 and 1988.

There were four patients with incomplete HDLR, in whom the left hepatic artery was preserved. In the remaining ten patients the hepatoduodenal ligament was resected *en bloc*. In one patient, despite complete HDLR, the left hepatic artery remained because it was a branch of the left gastric artery. Four of these ten patients did not have hepatic artery reconstruction; the right hepatic artery was reconstructed in two cases, the left artery in one case, and both hepatic arteries in two cases. Hepatic artery reconstruction was usually achieved with a graft of long saphenous vein to the common hepatic artery. For portal vein reconstruction, end-to-end anastomosis or a graft of common iliac vein was performed.

Blood flow in the bile duct was measured with a laser Doppler microflowmeter (LD6000 capillary perfusion monitor; Medpacific, Seattle, USA). The region of interest assessed by the probe is 1 mm^2 at a depth of 0·6–1·5 mm (References 3, 4). The laser probe was placed on the upper common bile duct and blood flow was compared before and after arterial occlusion.

Statistical analysis was performed by Student's *t* test as appropriate.

Results

The occurrence of anastomotic problems after choledochojejunostomy was related to the presence of blood flow in the hepatic artery (*Table 1*). Of the five patients with a preserved left hepatic artery, two had anastomotic leakage, while all four patients with resection of the right and left hepatic arteries without reconstruction developed anastomotic problems. However, in the five patients with reconstruction of the right or left hepatic artery, only one case of anastomotic leakage occurred.

There was a low (11 per cent) rate of anastomotic problems

Table 1 *Incidence of anastomotic leakage of choledochojejunostomy in relation to reconstruction or non-reconstruction of the hepatic artery*

Procedure	Hepatoduodenal ligament resection	Hepatectomy + PD	Hepatectomy	PD (or TP)
Hepatic artery not reconstructed	Incomplete (left hepatic artery preserved)	○ ●	○ ●	
	Complete	○*	● ●	● ●
Hepatic artery reconstructed	Complete	○	○ ●	○ ○

○, Case without anastomotic leakage; ●, case with anastomotic leakage; *accessory hepatic artery from left gastric artery was preserved. PD, pancreaticoduodenectomy; TP, total pancreatectomy

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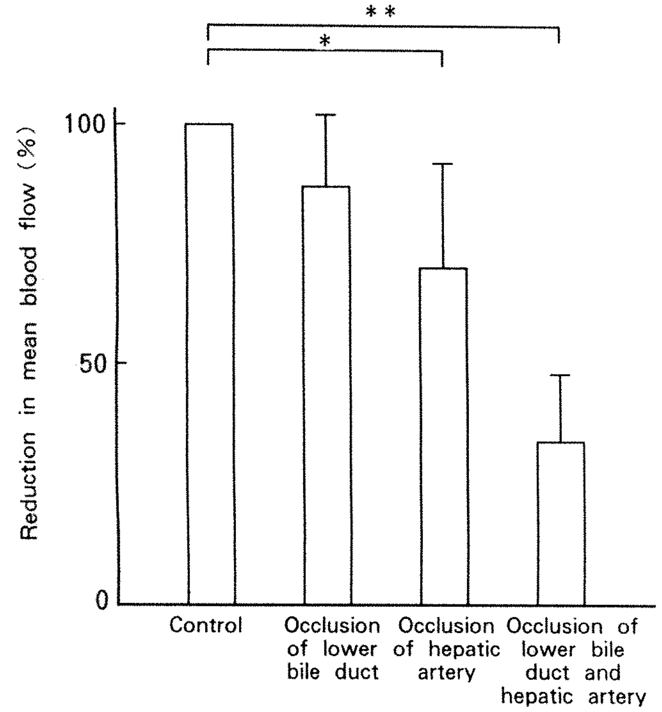

Figure 1 *Influence of occlusion of artery upon biliary blood flow* (n = 7). *$P<0{\cdot}05$; **$P<0{\cdot}01$ (*Student's* t *test*)

in 37 patients with cholangiocarcinoma who underwent choledochojejunostomy without hepatic artery resection, including three (23 per cent) of 13 who had liver resection alone or combined with pancreaticoduodenectomy.

The influence of hepatic artery occlusion on blood flow in the upper common bile duct was studied in seven patients. Occlusion of the arteries supplying the lower common bile duct reduced the mean(s.d.) blood flow to 88(14·8) per cent of the original level, although this was not significantly different. Occlusion of the hepatic artery reduced the mean(s.d.) flow to 70(21·4) per cent ($P<0{\cdot}05$), and when both the hepatic artery and the common bile duct were occluded, the mean(s.d.) blood flow fell to 34(14·3 per cent) of the original level ($P<0{\cdot}01$) (*Figure 1*). Occlusion of the portal vein had no effect on blood flow in the upper common bile duct.

After reconstruction of the right hepatic artery, this vessel was patent in all four cases, but the left hepatic artery was patent in only one of three cases.

Discussion

Damage during the operation has generally been implicated as a cause of postoperative complications such as bile duct stenosis or anastomotic leakage after choledochojejunostomy, although Appleby[5] pointed out that impairment of blood flow may be a possible cause. Since liver transplantation became more common, various biliary complications such as bile duct stenosis, anastomotic leakage and the accumulation of sludge in the bile duct stump have led to the recognition of the importance of the blood supply to the bile duct[6,7].

In the present study, anastomotic leakage following choledochojejunostomy occurred in all patients whose hepatic arteries were not reconstructed after resection of both main branches, whereas it was seen in only 20 per cent of patients in whom the arteries were reconstructed. Factors other than ischaemia should also be taken into account as a cause of anastomotic leakage after choledochojejunostomy, but in cases where the hepatic artery was not resected, the anastomotic leakage rate was 11 per cent, and following liver resection it was 23 per cent. These results suggest that the reduction in blood flow in the bile duct vessels after HDLR without reconstruction was related to the much higher rate of anastomotic leakage. Further support for the importance of hepatic arterial flow for the integrity of the bile duct is the report by Ogata[8] of a patient who developed intrahepatic bile duct necrosis while the liver parenchyma remained intact after embolization of the hepatic artery.

Northover and Terblanche[9] studied resin casts of the arterial supply of the bile duct taken from 24 cadavers. The principal arteries originated inferiorly from the retroduodenal, gastroduodenal and retroportal arteries, and superiorly from the right hepatic, cystic and left hepatic arteries. Arteries supplying the bile duct from the adjacent vessels were very few.

Capillary blood flow after occlusion of upwards flow along the lower common bile duct and occlusion of the proper hepatic artery fell to 34 per cent of normal. This is in accordance with the findings of Northover and Terblanche[9], and emphasizes the contribution of ischaemia to biliary leakage in patients in whom reconstruction of the hepatic artery was not carried out. We believe that reconstruction of the hepatic artery after HDLR is essential to minimize biliary anastomotic leakage. We also consider that the site of biliary resection should be close to the liver to reduce the incidence of complications.

As the left and right hepatic arteries communicate in the liver, hepatic artery reconstruction does not need to be carried out if only one artery is resected[8]. Theoretically, reconstruction of either hepatic artery may provide adequate revascularization, but in our experience patency after operation is better for the right hepatic artery than for the left, suggesting that right hepatic artery reconstruction may be safer.

References

1. Beazley RM, Hadjis N, Benjamin IS *et al.* Clinicopathological aspects of high bile duct cancer. *Ann Surg* 1984; **199**: 623–36.
2. Todoroki T, Okamura T, Fukao K *et al.* Gross appearance of carcinoma of the main hepatic duct and its prognosis. *Surg Gynecol Obstet* 1980; **150**: 33–40.
3. Bonner R, Nossal R. A model for laser Doppler measurement of blood flow in tissue. *Applied Optics* 1981; **20**: 2097–107.
4. Feld AD, Fondacaro JD, Holloway GA *et al.* Laser Doppler velocimetry: a new technique for the measurement of intestinal mucosal blood flow. *Gastrointest Endosc* 1984; **30**: 225–30.
5. Appleby LH. Indwelling common duct tube. *J Int Coll Surg* 1959; **31**: 631–43.
6. Starzl TE, Putham CW, Ishikawa M *et al.* Current policies in hepatic transplantation: candidacy of patients with alcoholic liver disease or preformed antidonor antibodies and a reappraisal of biliary duct reconstruction. *Ann NY Acad Sci* 1975; **252**: 145.
7. Calne RY, McMaster P, Portmann B *et al.* Observations on preservation, bile drainage and rejection in 64 human orthotopic liver allografts. *Ann Surg* 1977; **186**: 282–90.
8. Ogata Y. Application of vascular surgical technique for general surgery (in Japanese). *Shujutsu* 1988; **42**: 591–606.
9. Northover JMA, Terblanche J. A new look at the arterial supply of the bile duct in man and its surgical implications. *Br J Surg* 1979; **66**: 379–84.

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Factors influencing local recurrence and survival in patients with soft tissue sarcoma of the upper limb

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Fifty-one patients with soft tissue sarcoma of the upper limb were studied to identify risk factors for local recurrence and survival. More than half (53 per cent) of the patients referred had locally recurrent disease. The flexor aspect of the forearm was the most common site of origin. The majority of patients were managed by a combination of conservative surgery and radical radiotherapy. Wide or radical excision was achieved in 49 per cent of cases. One-third of patients required partial resection of bone or neurovascular structures; 75 per cent of them had presented with local recurrence after treatment elsewhere. Skin grafts and flap repairs were used more often in patients with local recurrence ($P = 0{\cdot}013$) *and 20 (74 per cent) of those referred with locally recurrent disease have had no further local relapse. The overall 5-year survival rate of 80 per cent (95 per cent confidence interval 61–90 per cent) supports a policy of conservative surgery. Factors associated with a lower survival rate were deep fixation, origin in the flexor aspect of the forearm, and previous local recurrence. Deep fixation was also associated with an increased risk of local recurrence. Referral to a specialist unit at the time of initial presentation may result in lower rates of local recurrence and may improve the survival rate.*

Soft tissue sarcomas of the upper limb are uncommon, accounting for between 13 and 15 per cent of these tumours at all sites[1,2]. They present a challenging problem in terms of maintaining adequate function and avoiding amputation[3,4].

Although limb conservation by a combination of surgery and radiotherapy is usually possible[5], it is technically more difficult than in the lower limb because neurovascular structures are closer together and there is less muscle bulk for adequate clearance[6,7]. Several authors have reported a higher rate of local recurrence after limb-sparing surgery than after amputation[8,9] but whether or not this influences survival is controversial[8,10,11].

The aims of this study were to establish the prognostic factors influencing local recurrence and survival rates in patients with soft tissue sarcoma of the upper limb and to evaluate the influence of local recurrence itself on the survival rate.

Patients and methods

Between 1980 and 1990, 74 patients with upper limb sarcomas (excluding the shoulder girdle) were seen. Two patients had primary bone tumours, one a childhood rhabdomyosarcoma, and 20 were referred for a second opinion alone and did not undergo further treatment at this hospital; these patients were excluded from further analysis.

Of 51 patients managed definitively, 24 were referred with previously untreated soft tissue sarcomas: five had only a presumptive diagnosis of sarcoma (i.e. no histological diagnosis), nine had undergone incision biopsy, and ten excision biopsy. In the five patients referred without histological diagnosis, this was established by Tru-Cut® (Travenol Laboratories Incorporated, Deerfield, Illinois, USA) biopsy.

Twenty-seven patients were referred for management of locally recurrent disease after definitive management at other institutions. Of these, 12 had suffered one recurrence, ten two recurrences, four three recurrences, and one four previous recurrences. The median time interval between initial diagnosis and referral was 30 months (range 3–312 months). In three patients the time interval to recurrence was greater than 14 years.

No patient had a history of lymphoedema, neurofibromatosis or irradiation to the limb. The median age of patients was 46 years (range 5–76 years); 28 were men and 23 were women.

The site and size of the tumour at definitive presentation were recorded. Proximal tumours were defined as those arising above but excluding the elbow.

Treatment

Management policy is to undertake limb-sparing surgery whenever possible and to give radiotherapy to all patients with high-grade or recurrent tumours and to those with intermediate or low-grade tumours in whom satisfactory surgical clearance is not achieved[12]. Preoperative irradiation is employed in patients with rapidly growing high-grade tumours which have limited mobility on clinical examination or are unlikely to be excised with a wide margin of clearance judging by appearances on computed tomography (CT). Regional chemotherapy is rarely used except for palliation.

Margins of surgical clearance are defined according to criteria described by Enneking *et al.*[13]. Radical clearance is defined as complete excision of the compartment containing the tumour or amputation above the level of the compartment. Wide excision indicates a margin of tissue around the sarcoma without macroscopic or microscopic evidence of tumour infiltration. Marginal excision is recorded if the tumour pseudocapsule is seen at operation, and intracapsular excision is recorded if the capsule is breached.

'Adequate' surgery includes radical and wide excision while 'inadequate' surgery includes marginal and intracapsular excision. These terms apply whether or not limb conservation is achieved.

Pathology

Histological diagnoses and tumour grades were reviewed by one pathologist (C.F.). Grade was usually determined from an estimate of the extent of tumour necrosis, cellularity, pleomorphism, degree of differentiation and mitotic index, but in some cases it was determined by the diagnosis; synovial sarcoma, for example, was always considered to be high grade. Immunohistochemistry and electron microscopy were performed if suitable tissue was available[14].

Survival and statistics

The patients have been followed up for a median of 46 months (range

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Table 1 *Site of upper limb sarcomas*

Site	No.
Deltoid	2
Upper arm	
Flexor	8
Extensor	7
Elbow/antecubital fossa	9
Forearm	
Flexor	16
Extensor	4
Hand	5
Total	51

Table 2 *Histology and grade of upper limb sarcomas*

	Grade			
Histology	Low	Intermediate	High	Total
Malignant fibrous histiocytoma	5	3	6	14
Synovial sarcoma			13	13
Epithelioid sarcoma			3	3
Clear cell sarcoma			1	1
Liposarcoma	3		3	6
Sarcoma (not otherwise specified)			5	5
Extraskeletal myxoid chondrosarcoma	2			2
Malignant peripheral nerve sheath tumour	1	1	1	3
Leiomyosarcoma		1		1
Malignant haemangio-pericytoma	1			1
Epithelioid haemangio-endothelioma	1			1
Rhabdomyosarcoma			1	1
Total	13	5	33	51

5–290 months) from the date of definitive presentation. Patients were seen at 3-monthly intervals for 2 years after treatment, at 6-monthly intervals for a further 3 years, and annually thereafter. Follow-up included regular chest radiography and CT of the thorax.

Local recurrence-free survival, disease-free survival and overall survival rates were calculated from the date of definitive presentation according to the method of Kaplan and Meier[15]. Five-year survival probabilities are given as percentages with 95 per cent confidence intervals (CI). The log rank test was used to compare differences between subgroups.

The following factors were evaluated in multivariate analyses of risk factors for overall survival, disease-free survival and local recurrence-free survival rates (for the 51 patients): sex; age; local recurrence before presentation; site (proximal *versus* distal); maximal tumour diameter at presentation; deep fixation on clinical examination; relationship to the deep fascia; surgical excision margins (adequate *versus* inadequate) achieved definitively; invasion requiring resection of bone, vessel or nerve; histological subtype (malignant fibrous histiocytoma or synovial or other sarcoma); tumour grade (high or intermediate *versus* low); and radiotherapy. The data were analysed by Cox's proportional hazards model[16].

Results

Clinical and pathological features

The sites of tumours are given in *Table 1*. The most common site was the flexor aspect of the forearm. Deep fixation was observed in 14 of the 51 tumours. The median maximum tumour diameter was 5 cm (range 1–18 cm). The tumour was superficial to the deep fascia in six patients, deep to the deep facia in 43, and unknown in two. On definitive presentation, six patients had pulmonary metastases (two in the previously untreated group and four in those referred with local recurrence). *Table 2* lists the histological subtypes and tumour grades. Thirty-three tumours (65 per cent) were high grade.

Surgery

The definitive surgical procedures performed are listed in *Table 3*. There was histological evidence of residual disease in three of six patients who had re-excision of the tumour bed after excision biopsy performed elsewhere. Thirty-five patients had major soft tissue resections. Radical excision was performed in six patients (one amputation and five compartmental resections with limb preservation) and wide excision in 19, resulting in adequate clearance in 49 per cent of cases. Marginal excision was performed in 21 patients.

The proportion of patients undergoing adequate surgery was similar for those with previously untreated or recurrent tumours. In those with local recurrence, the margins of the original resection performed elsewhere before referral were: intracapsular, five; marginal, 16; wide, two; radical, none; and unknown, four.

Sixteen patients had invasion of bone or neurovascular structures which required resection. Seven required partial excision of bone to achieve tumour clearance: the epicondyles or anterior cortex of the humerus in three patients, the proximal or distal radius or ulna in four. A further four patients had major nerves excised in continuity with the tumour (ulnar, two; posterior interosseous, one; musculocutaneous, one), and two required resection of arteries (radial or ulnar). Twelve (75 per cent) of these 16 patients were in the group with local recurrence. In an additional eight patients, vessels or nerves were grossly displaced by the tumour but did not require resection. Five patients underwent amputation as the primary surgical treatment; three required metacarpal/ray amputations for tumours arising in the hand which were classified as wide excisions. One patient underwent an above-elbow amputation which constituted a radical resection. In one patient a forequarter amputation for otherwise untreatable local disease was performed but clearance was marginal.

Only two previously untreated patients required skin grafting to achieve wound closure. Of those with recurrent tumours, six required skin grafting and four required free vascularized latissimus dorsi flap repairs for locally recurrent disease at the elbow ($\chi^2 = 5\cdot82$, $P = 0\cdot013$).

Radiotherapy

Thirty-seven patients received radiotherapy after referral (*Table 4*). Four received radiotherapy alone because conservative excision was technically impossible. Fourteen patients did not receive radiotherapy, because of previous irradiation in ten, low tumour grade in two and the presence of metastatic disease in two. The median dose of radiation given before operation was 58·0 Gy (mean 53·8, range 40–62 Gy), all but one patient receiving 2 Gy/day. The median dose given after operation or after biopsy alone was 60·0 Gy (mean 54·5, range 40–63 Gy), all but six patients receiving 2 Gy/day. One patient received treatment with neutrons (15·6 Gy in 12 fractions).

Table 3 *Definitive surgery for all patients*

Procedure	Previously untreated tumours	Recurrent tumours	Total
Biopsy alone	2	3	5
Re-excision of tumour bed	6	–	6
Soft part resection	12	16	28
Soft part resection and partial bony resection	1	6	7
Amputation			
Metacarpal/ray	2	1	3
Above elbow	1	0	1
Forequarter	0	1	1
Total	24	27	51

Chemotherapy

Three patients received intra-arterial chemotherapy with doxorubicin; this was the sole treatment in one patient with recurrence. Six patients received systemic doxorubicin and ifosfamide for metastatic disease.

Local recurrence

Twelve patients developed local recurrence after definitive treatment. Five were from the previously untreated group and seven had presented with local recurrence. Thus 20 (74 per cent) patients referred with local recurrence have had no further local relapse.

The probability of survival without local recurrence at 5 years was 54 per cent (95 per cent CI 22–78 per cent) for tumours with deep fixation, and 87 per cent (95 per cent CI 70–95 per cent) for those without deep fixation ($P = 0{\cdot}005$) (*Figure 1*). Multivariate analysis showed deep fixation and a diagnosis of malignant fibrous histiocytoma to be associated with an increased risk of local recurrence (*Table 5*).

The 12 patients who developed local recurrence after definitive treatment underwent a total of 16 additional salvage surgical procedures for local recurrence: 11 soft part resections, one debulking, and four above-elbow amputations.

Amputation

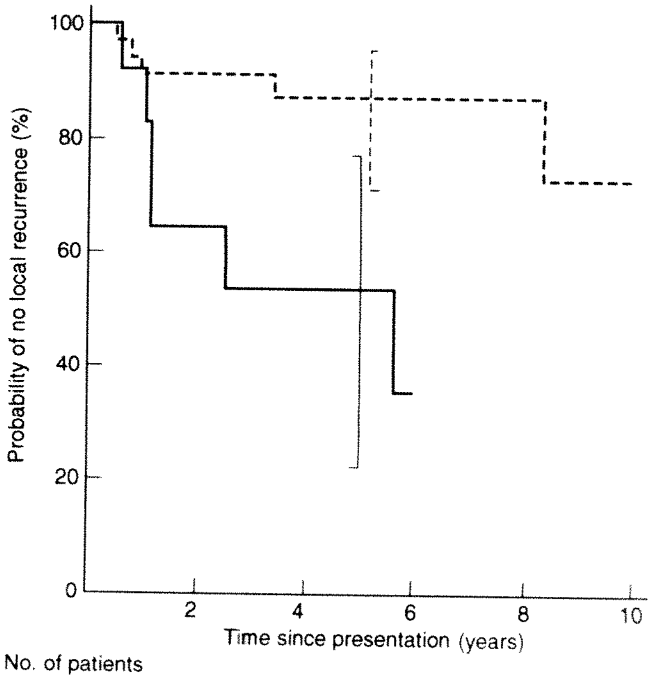
Five above-elbow and one forequarter amputations were performed. They were all undertaken for uncontrolled local recurrence after previous limb-sparing surgery and radical radiotherapy. Amputation was performed in the presence of distant metastases in two patients for palliation of ulcerating local disease. The margins of clearance obtained by amputation were marginal in four and radical in two. Four of the six amputees have died. Two died with further local recurrence in the amputation stump. Neither of the two amputees who are alive has stump recurrence; one has pulmonary metastases and the other is currently disease-free.

Survival

Ten patients have died from disseminated disease; three from the previously untreated group and seven who presented with local recurrence. The probability of 5-year survival for the total series was 80 per cent (95 per cent CI 61–90 per cent). The probability of 5-year survival for patients without metastases at presentation (85 per cent; 95 per cent CI 65–94 per cent) was significantly greater than that for patients with metastases (25 per cent; 95 per cent CI 1–66 per cent) (log rank test, $\chi^2 = 30{\cdot}36$, $P < 0{\cdot}005$). When the six patients with metastases on presentation were excluded from the survival analysis, three other independent risk factors were identified (*Table 5*). The probability of 5-year survival with deep fixation on clinical examination was 52 per cent (95 per cent CI 14–80 per cent), significantly less than for those without fixation (88 per cent; 95 per cent CI 67–96 per cent; $P = 0{\cdot}003$; *Figure 2*). The other two risk factors predictive of poor survival were a tumour of the flexor aspect of the forearm and previous local recurrence before presentation. Previous local recurrence ($\chi^2 = 5{\cdot}5$, $P = 0{\cdot}02$) and deep fixation ($\chi^2 = 14{\cdot}4$, $P = 0{\cdot}0001$) were also associated with a lower disease-free survival rate on multivariate analysis.

Table 4 *Radiotherapy: relationship to surgery and recurrent disease*

Treatment group	Primary treatment ($n = 24$)	Local recurrence ($n = 27$)
Radiotherapy alone	2	2
Preoperative radiotherapy	10	3
Postoperative radiotherapy	8	12
No radiotherapy	4	10



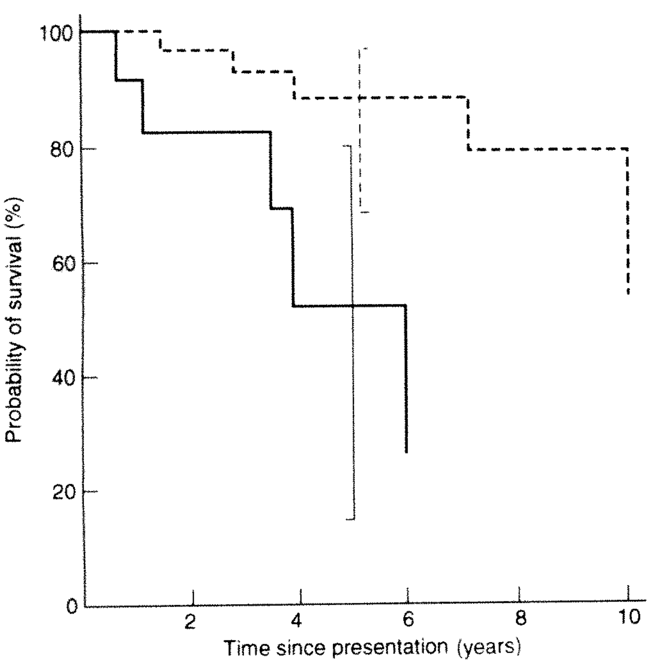
No. of patients at risk					
--- 37	26	20	12	6	2
—— 14	7	3	1	0	0

Figure 1 *Local recurrence-free survival rate for 51 patients with soft tissue sarcoma of the upper limb. ——, Patients with deep fixation; -----, patients without deep fixation. The numbers of patients at risk at each time interval are shown, as are the 95 per cent confidence intervals (log rank test, $\chi^2 = 7{\cdot}73$, P = 0·005)*

Table 5 *Significant risk factors* for local relapse and survival*

Factor	Hazard for	Relative to	Hazard ratio†	Probability	
				χ^2	P
Local relapse					
Deep fixation	Present	Absent	9·9 (2·3–42·0)	10·03	0·0015
Histology	Malignant fibrous histiocytoma	Other histology	5·1 (1·3–19·7)	5·30	0·02
Survival‡					
Previous local recurrence	Previous local recurrence	No local recurrence	10·6 (1·3–86·9)	6·50	0·01
Site	Flexor forearm	Other sites	6·4 (1·02–40·0)	4·73	0·03
Deep fixation	Present	Absent	21·4 (3·04–150·8)	11·61	0·0007

* Other factors tested were: sex, age, maximum tumour diameter, relationship to deep fascia, surgical excision margins, invasion of bone, vessel or nerve, tumour grade and radiotherapy. † Values in parentheses are 95 per cent confidence intervals; ‡ results of analysis with 'presence of metastases' withdrawn as a covariate



No. of patients at risk					
--- 37	27	21	13	6	2
—— 14	8	4	1	0	0

Figure 2 *Overall survival rate for 51 patients with soft tissue sarcoma of the upper limb.* ——, *Patients with deep fixation;* -----, *patients without deep fixation. The numbers of patients at risk at each time interval are shown, as are the 95 per cent confidence intervals (log rank test,* $\chi^2 = 8{\cdot}61$, *P = 0·003)*

Discussion

Loss of the upper limb, especially loss of the dominant limb, is a major disability. Available prostheses compensate poorly for this loss[6]. Whenever possible, soft tissue sarcoma of the upper limb should be treated by a combination of limb-sparing surgery and radical radiotherapy. The results of this approach in terms of local recurrence and overall survival are equivalent to those obtained by amputation alone[3,4,17–22].

In the present series the flexor aspect of the forearm was the commonest site of tumours. Others have reported a greater proportion of proximal tumours[2,9]. The reason for this disparity is uncertain. A further disparity was the lower survival rate in patients with tumours of the flexor aspect of the forearm, which contrasts with reports that more proximal tumours tend to be larger on detection and have a worse prognosis[8,9,11,20]. Although no correlation between the site of the tumour and its size at presentation was evident in this study, the precise dimensions of the original tumour in those with recurrence was unknown.

Of the 24 patients with non-recurrent soft tissue sarcoma, five were referred with a presumptive diagnosis alone and in these the diagnosis was established by Tru-Cut needle biopsy under local anaesthesia at the initial consultation as previously described[23]. Ten patients had previously been treated by local excision biopsy (enucleation) but this method of diagnosis is less satisfactory because anatomical planes are disturbed, making it impossible to determine the exact site of the primary tumour.

The commonest tumour types, as in other series, were malignant fibrous histiocytoma and synovial sarcoma and liposarcoma[8,24]. All histological diagnoses were reviewed by one pathologist (C.F.) and, although in some cases the terminology changed (for example from fibrosarcoma to malignant fibrous histiocytoma), the histology of recurrent tumours was the same as that of the primary tumour. For tumours whose grade is not dictated by their histology there was a tendency for recurrent tumours to be of higher grade.

All three patients with recurrent tumours occurring after a period of more than 14 years had synovial sarcomas, which by definition are high grade. Although they were all treated initially with a combination of surgery and radiotherapy it is likely that they represented true recurrences rather than radiation-induced sarcomas as the histology of the recurrence was the same as that of the primary tumour.

Adequate surgical clearance was achieved in 49 per cent of cases, identical to that reported by Collin *et al.*[9]. The proportion is less than that achieved in the lower limb because of the greater difficulty in obtaining wide excision margins, especially in sites such as the flexor aspect of the forearm where neurovascular structures run closely together and available muscle bulk is limited. Adjuvant radical radiotherapy is therefore essential for adequate local treatment of upper limb soft tissue sarcomas[25,26].

As previously reported[27], compartmental resection is possible in only 15 per cent of cases of extremity sarcoma because many tumours are extracompartmental, arising in areas not confined by fascial boundaries, such as the antecubital fossa or the subcutaneous plane, or arising at an intercompartmental boundary. In the event of local recurrence, tumour boundaries may become indistinct, reducing the likelihood of performing a satisfactory compartmentectomy[28].

Approximately one-third of the patients required partial resection of bone or neurovascular structures. Nevertheless, limb-sparing surgery was usually possible and a functional limb was retained in most cases. Three-quarters of these patients had had previous local recurrences. With each episode of local recurrence the likelihood of sacrificing a major structure or of amputation increases[6] and so it is important to optimize initial treatment[8,20]. It has been confirmed that, if local recurrence occurs, further limb-sparing surgery remains possible[29] but after multiple local recurrences amputation may become necessary.

Results also confirm that (when previous surgery is judged to have been adequate) re-excision of the tumour bed yields residual tumour in 50 per cent of re-excision specimens[19]. The decision to re-excise the tumour bed is based on the details of previous surgery, the histological excision margins and the length of the skin incision in relation to the reported size of the original tumour[6,18].

Skin grafting and free microvascular flap repair are more likely to be needed after limb-sparing surgery for local recurrence, especially for tumours around the elbow where there is little soft tissue available to achieve primary wound closure[30]. Expertise in reconstructive procedures should be readily available.

Multivariate analysis for local recurrence revealed that, although deep fixation was a major independent risk factor, previous local recurrence was not, in contrast to reports from elsewhere[9,31]. The failure of local recurrence to emerge as an independent predictor of further relapse after treatment may be explained by the high proportion of patients in whom adequate surgical excision was achieved after referral. Although less than a quarter of those with locally recurrent disease at presentation had undergone adequate primary surgery, radical or wide excision was subsequently achieved in 49 per cent of the total series, including those with local recurrence, 74 per cent of whom remained free of further relapse. The apparent lack of influence of local recurrence thus reflects the success of re-excision in the present series. Likewise, inadequate surgical margins and invasion of local structures, which correlated with local recurrence in other studies[21,32], were not identified as independent risk factors, probably for the same reason.

The overall 5-year survival rate of 80 per cent compares favourably with rates of between 40 and 60 per cent reported in other series of soft tissue sarcomas of the limbs[8]. This may be partly explained by exclusion of tumours of the shoulder girdle which carry a poor prognosis (probably because of their large size) and may mask the importance of other prognostic factors[8,20,28]. The 5-year survival rate supports a policy of limb-sparing surgery, especially as further limb-sparing procedures are possible if there is local recurrence.

The presence of metastases at presentation is a major risk factor predictive of poor survival[2,20]. When patients with metastases were excluded from the analysis, however, three independent risk factors associated with a low overall survival rate were identified (deep fixation, a tumour arising in the flexor aspect of the forearm, and previous local recurrence). Deep fixation and previous local recurrence have been reported by others[11,24,33] to predict poor survival, and in this series they were also associated with a lower disease-free survival rate.

Adequate clearance margins are more difficult to achieve around the elbow and in the forearm and hand than in the upper arm and deltoid regions. In this series excision margins achieved in the forearm were minimal, and this may explain why, on multivariate analysis, the flexor aspect of the forearm emerged as a more important factor than excision margins in predicting survival. Tumour size and grade and inadequate surgical margins have correlated with survival in other reports, but not in the present analysis[8,21,33,34].

More than half (53 per cent) of the patients were referred with local recurrence. Only four (15 per cent) of these patients had metastatic disease, indicating that they are probably a selected group. It has been suggested that patients who survive several episodes of local recurrence without developing metastases may be in a better prognostic category than others[6] and that the development of local recurrence does not prejudice survival[6,8,10]. Others have suggested that local recurrence may reduce survival because of an increased risk of tumour dissemination[2,11,32,35,36], and the current series (although of small numbers) appears to confirm this. In the head, neck and retroperitoneum, sarcomas are difficult to excise with a satisfactory margin and are prone to recur locally, causing death from the effects of local disease. Soft tissue sarcomas of the upper limb, however, do not cause death from uncontrolled local disease and the finding of a lower survival rate associated with previous local recurrence is therefore noteworthy.

In conclusion, patients with soft tissue sarcomas should be treated in specialist units. Adequate surgery and radiotherapy to treat the initial primary tumour and conserve the upper limb are likely to result in a lower rate of local recurrence, which in turn may result in an improved survival rate.

References

1. Brennan MF. Management of extremity sarcomas. *Aust NZ J Surg* 1988; **58**: 693–702.
2. Creighton JJ, Peimer CA, Mindell ER, Boone DC, Costantino CP, Douglass HO. Primary malignant tumours of the upper extremity: retrospective analysis of one hundred twenty-six cases. *J Hand Surg (Am)* 1985; **10**: 805–14.
3. Suit HD, Mankin HJ, Wood WC, Proppe KH. Preoperative, intraoperative, and postoperative radiation in the treatment of primary soft tissue sarcoma. *Cancer* 1985; **55**: 2659–67.
4. Lindberg RD, Martin RG, Romsdahl MM, Barkley HT. Conservative surgery and postoperative radiotherapy in 300 adults with soft-tissue sarcoma. *Cancer* 1981; **47**: 2391–7.
5. Brennan MF. Management of soft tissue sarcoma. *Aust NZ J Surg* 1990; **60**: 419–28.
6. Westbury G. Surgery in the management of soft tissue sarcoma. *Clin Oncol* 1989; **1**: 101–5.
7. Okunieff P, Suit HD, Phil D, Proppe KH. Extremity preservation by combined modality treatment of sarcomas of the hand and wrist. *Int J Radiat Oncol Biol Phys* 1986; **12**: 1923–9.
8. Potter DA, Kinsella T, Glatstein E *et al.* High-grade soft tissue sarcomas of the extremities. *Cancer* 1986; **58**: 190–205.
9. Collin C, Hajdu SI, Godbold J, Friedrich C, Brennan MF. Localised operable soft tissue sarcoma of the upper extremity. *Ann Surg* 1987; **205**: 331–9.
10. Rosenberg SA, Tepper J, Glatstein E *et al.* The treatment of soft tissue sarcomas of the extremities: prospective randomised evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. *Ann Surg* 1982; **196**: 305–15.
11. Stotter AT, A'Hern RP, Fisher C, Mott AF, Fallowfield ME, Westbury G. The influence of local recurrence of extremity soft tissue sarcoma on metastasis and survival. *Cancer* 1990; **65**: 1119–29.
12. Robinson MH, Barr LC, Fisher C *et al.* Treatment of extremity soft tissue sarcomas with surgery and radiotherapy. *Radiother Oncol* 1990; **18**: 221–33.
13. Enneking WF, Spanier SS, Malawer MM. The effect of anatomic setting on the results of surgical procedures for soft part sarcomas of the thigh. *Cancer* 1981; **47**: 1005–22.
14. Fisher C. The value of electron microscopy and immunohistochemistry in the diagnosis of soft tissue sarcomas: a study of 200 cases. *Histopathology* 1990; **16**: 441–54.
15. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; **8**: 423–46.
16. Cox DR. Regression models and life-tables. *J R Statist Soc* 1972; **B34**: 197–202.
17. Eilber FR, Mirra JJ, Grant TT, Weisenburger T, Morton DL. Is amputation necessary for sarcomas? *Ann Surg* 1980; **192**: 431–7.
18. Westbury G. Surgery of soft tissue sarcomas. In: Pinedo HM, Verweij J, eds. *Treatment of Soft Tissue Sarcomas*. 1st ed. Boston: Kluwer Academic Publishers, 1989: 51–64.
19. Suit HD, Mankin HJ, Wood WC *et al.* Treatment of the patient with stage Mo soft tissue sarcoma. *J Clin Oncol* 1988; **6**: 854–62.
20. Brennan MF. The management of soft tissue sarcomas. *Br J Surg* 1984; **71**: 964–7.
21. Brennan MF, Shiu MH. Presentation, demographics, and prognosis. In: Shiu MH, Brennan MF, eds. *Surgical Management of Soft Tissue Sarcomas*. Philadelphia: Lea and Febiger, 1989: 45–57.
22. Karakousis CP, Emrich LJ, Rao U, Krishnamsetty RM. Feasibility of limb salvage and survival in soft tissue sarcoma. *Cancer* 1986; **57**: 484–91.
23. Ball ABS, Fisher C, Pittam M, Watkins RM, Westbury G. Diagnosis of soft tissue tumours by Tru-Cut biopsy. *Br J Surg* 1990; **77**: 756–8.
24. Collin C, Godbold J, Hajdu SI, Brennan MF. Localised extremity soft tissue sarcoma: analysis of factors affecting survival. *J Clin Oncol* 1987; **5**: 601.
25. Leibel SA, Tranbaugh RF, Wara WM, Beckstead JH, Bovill EG, Phillips TL. Soft tissue sarcomas of the extremities. Survival and patterns of failure with conservative surgery and postoperative irradiation compared to surgery alone. *Cancer* 1982; **50**: 1076–83.
26. Shiu MH, Hajdu SI. Management of soft tissue sarcoma of the extremity. *Semin Oncol* 1981; **8**: 172–9.
27. Stotter AT, Fallowfield ME, Mott A, Fisher C, Westbury G. Role of compartmental resection for soft tissue sarcoma of the limb and limb girdle. *Br J Surg* 1990; **77**: 88–92.
28. Barr LC, Robinson MH, Fisher C, Fallowfield ME, Westbury G. Limb conservation for soft tissue sarcomas of the shoulder and pelvic girdles. *Br J Surg* 1989; **76**: 1198–201.
29. Giuliano AE, Eilber FR, Morton DL. The management of locally recurrent soft tissue sarcoma. *Ann Surg* 1982; **196**: 87–91.
30. Stotter AT, McLean NR, Fallowfield ME, Breach NM, Westbury G. Reconstruction after excision of soft tissue sarcoma of the limbs and trunk. *Br J Surg* 1988; **75**: 774–8.
31. Simon MA, Enneking WF. The management of soft-tissue sarcomas of the extremities. *J Bone Joint Surg (Am)* 1976; **58**: 317–27.
32. Markhede G, Angervall L, Stener B. A multivariate analysis of the prognosis after surgical treatment of soft tissue tumours. *Cancer* 1982; **49**: 1721–33.
33. Owens JC, Shiu MH, Smith R, Hajdu SI. Soft tissue sarcomas of the hand and foot. *Cancer* 1985; **55**: 2010–18.
34. Rooser B, Attewell R, Berg NO, Rydholm A. Prognostication in soft tissue sarcoma. A model with four risk factors. *Cancer* 1988; **61**: 817–23.
35. Cantin J, McNeer GP, Chu FC, Booher RJ. The problem of local recurrence after treatment of soft tissue sarcoma. *Ann Surg* 1968; **168**: 47–53.
36. Bramwell VHC, Crowther D, Deakin DP, Swindell R, Harris M. Combined modality management of local and disseminated adult soft tissue sarcomas: a review of 257 cases seen over 10 years at the Christie Hospital and Holt Radium Institute, Manchester. *Br J Cancer* 1985; **51**: 301–18.

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Case report

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Management of coeliac artery aneurysms

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Only 4 per cent of all splanchnic artery aneurysms involve the coeliac axis[1]. Modern imaging techniques such as ultrasonography, computed tomography (CT) and digital subtraction angiography have allowed a greater diagnosis of such aneurysms[2]. A literature review by Graham *et al.*[3] cited 108 cases of coeliac artery aneurysm up to 1985, since when a further ten patients have been reported. We present here two interesting cases occurring in relatively young patients, one associated with tumoral calcinosis, the other with Crohn's disease.

Case reports

Case 1

A 36-year-old Iranian man with a 17-year history of the autosomal dominant disorder tumoral calcinosis presented with upper epigastric pain and a pulsatile mass in the abdomen. There was a history of surgery for septic arthritis of the left elbow, recurrent renal calculi and removal of periarticular nodules. Of four siblings, the elder sister had similar problems but two brothers were unaffected. While under the care of the metabolic unit, hyperphosphataemia associated with tumoral calcinosis was successfully treated with aluminium hydroxide, effectively producing a negative phosphorus balance.

Examination revealed the presence of a large aneurysm in the epigastrium and two associated aneurysms of the right brachial artery. Aortography showed an 8·5-cm diameter aneurysm of the coeliac axis involving the common hepatic as well as splenic arteries (*Figure 1*), although lateral views revealed the initial 2·5 cm of the coeliac axis origin to be normal (*Figure 2*). There were also aneurysms of both external iliac arteries (*Figure 1*).

At operation, in addition to the known aneurysms, the gastroduodenal, gastroepiploic and superior pancreaticoduodenal arteries were found to be aneurysmal. The aneurysms were excluded, necessitating splenectomy and an autogenous saphenous vein interposition graft between the coeliac axis origin and hepatic artery. Histology of the coeliac aneurysm sac showed myxoid degeneration with thrombosis. Postoperative recovery was uneventful.

Case 2

A 40-year-old woman was referred to the vascular unit on discovery of a saccular coeliac axis aneurysm during ultrasonographic screening for right-sided abdominal pain. Past medical history included hysterectomy for carcinoma of the cervix, and multiple small and large bowel resections for Crohn's disease. Aortography revealed a trilocular saccular aneurysm involving mainly the right wall of the coeliac axis (*Figure 3*). At operation, lateral coeliac aneurysmorrhaphy was performed using a cardiovascular expanded polytetrafluoroethylene patch. Histology of the aneurysm sac showed hypertrophy and fibrosis of the smooth muscle layer with marked active chronic inflammation. The patient made an uneventful recovery.

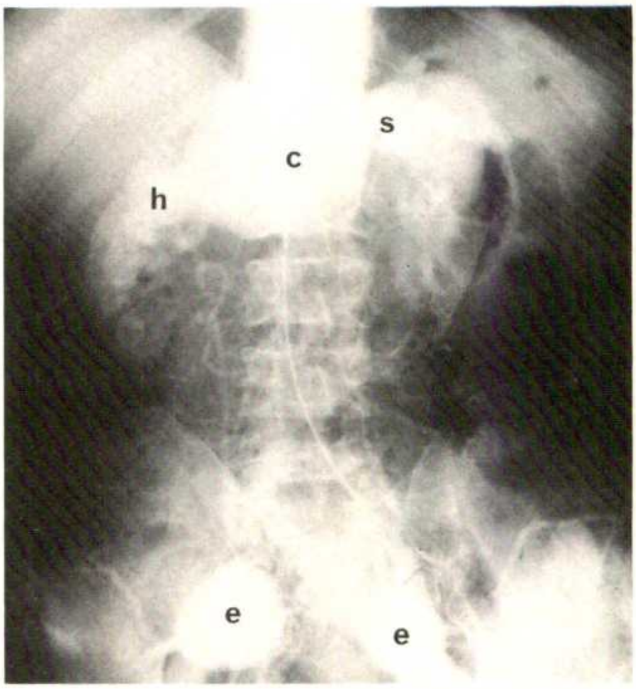

Figure 1 *Aortogram showing hepatic (h), coeliac (c), splenic (s) and external iliac (e) aneurysms in case 1.* © *University Department of Medical Illustration, Manchester Royal Infirmary*

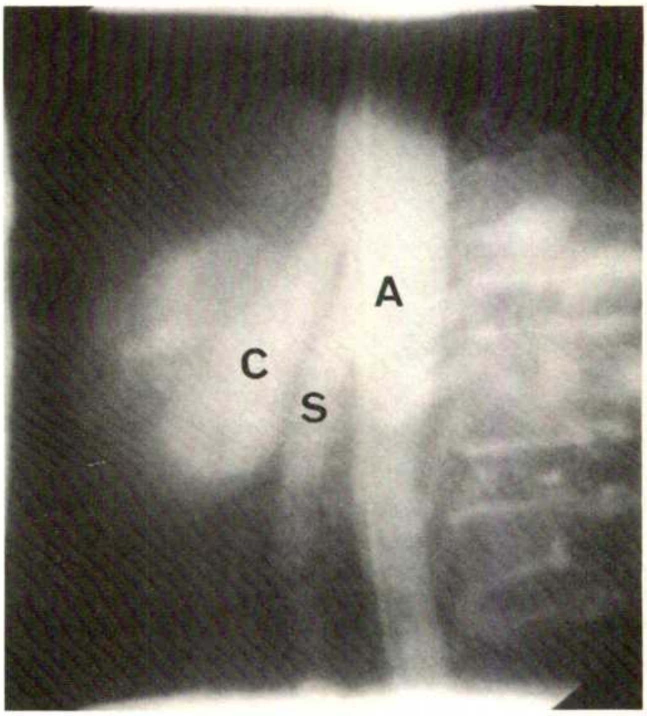

Figure 2 *Lateral aortogram showing the normal origin of the coeliac axis (C) in relation to the abdominal aorta (A) and superior mesenteric artery (S) in case 1.* © *University Department of Medical Illustration, Manchester Royal Infirmary*

Discussion

Graham *et al.*[3] reviewed 108 cases of coeliac artery aneurysm occurring between 1745 and 1984, including nine of their own. Of 60 aneurysms reported before 1950, 40 per cent were due to infection, 87 per cent had ruptured and 95 per cent were diagnosed only after death. Of the remaining 48 aneurysms reported since 1950, 13 per cent ruptured; 43 patients underwent operation, with a successful outcome in 91 per cent of cases[3].

Since 1985 a further 12 cases, including our two, have been reported[2,4–8]. Five cases were due to fibrous dysplasia, three

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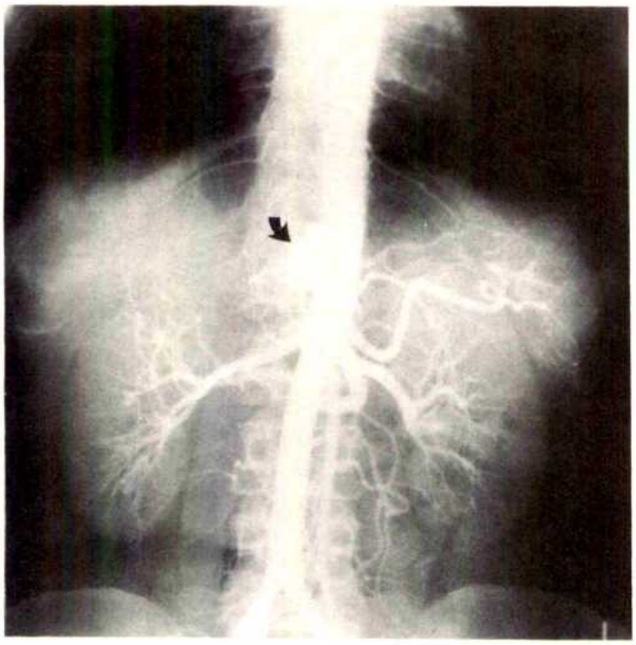

Figure 3 *Aortogram showing a trilocular saccular aneurysm in the right lateral wall of the coeliac axis (arrow) in case 2. © University Department of Medical Illustration, Manchester Royal Infirmary*

having associated pathology in the arcuate ligament, whereas only two cases were due to fibrous dysplasia in the series of 48 reported between 1950 and 1985[3]. Associated vascular disease was common before 1985, 18 per cent of cases having concomitant aortic aneurysm, with splanchnic aneurysms in 38 per cent[3]. Fifty per cent of the cases seen in the last 5 years had associated splanchnic aneurysms, with aneurysm of the abdominal aorta in 17 per cent.

Although six of these 12 patients presented with severe abdominal pain, four were completely asymptomatic and in two aneurysms were detected only incidentally on routine ultrasonographic examination. In comparison, 78 per cent of the 48 patients reported in the 35 years before 1985 were symptomatic, 61 per cent presenting with abdominal pain[3]. The incidence of rupture was 87 per cent before 1950, 13 per cent since 1950 and nil since 1985. All patients in the most recent group were diagnosed angiographically, with confirmation on ultrasonography or CT scan in half of them.

Table 1 *Symptoms, investigations and operative findings in coeliac artery aneurysms reported since 1985*

Case no.	Reference	Age (years)	Sex	Presentation	Investigation	Pathology	Procedure	Outcome
1	Wolf *et al.*[2]	52	M	Epigastric pain	Angiography, CT scan	Atheroma	Aneurysmectomy, 85% pancreatectomy, hepatic artery to coeliac artery anastomosis	Alive and well
2*	Flageat *et al.*[4]	42	F	Right hypochondrial pain	Angiography, CT scan, ultrasonography scan	Fibrous dysplasia, arcuate ligament	1. Aneurysmectomy and end-to-end anastomosis of hepatic artery 2. Aneurysmectomy and ligation of coeliac artery and hepatic artery	Alive and well
3	Lubbers *et al.*[5]	44	M	Right upper quadrant pain	Angiography, CT scan	Fibrous dysplasia	Aneurysmectomy and microvel graft	Alive and well
4	Kazui *et al.*[6]	50	M	Incidental on ultrasonography	Angiography, CT scan, ultrasonography scan	Fibrous dysplasia	Aneurysmectomy and interposition vein graft between coeliac artery and hepatic artery	Alive and well
5	Melliere *et al.*[7]	56	M	Incidental	Angiography	Atheroma	Aneurysmectomy and aortocoeliac ePTFE graft and aortobifemoral graft	Alive and well
6	Melliere *et al.*[7]	52	M	Abdominal pain	CT scan	Arcuate ligament	Aneurysmectomy and ePTFE graft between coeliac artery and hepatic artery	Alive and well
7	Melliere *et al.*[7]	41	F	Abdominal pain	Angiography	Arcuate ligament	Exclusion of aneurysm and aortocoeliac ePTFE graft	Alive and well
8	Geelkerken *et al.*[8]	56	M	Asymptomatic	Angiography	Atheroma	Aneurysmectomy and reimplantation of coeliac artery to aorta	Died from myocardial infarction
9	Geelkerken *et al.*[8]	63	M	Asymptomatic	Angiography	Atheroma	Aneurysmectomy and reimplantation of coeliac artery to aorta	Alive and well
10	Geelkerken *et al.*[8]	52	M	Asymptomatic	Angiography	Atheroma	Aneurysmectomy and end-to-end anastomosis of coeliac artery	Alive and well
11	Present case 1	36	M	Epigastric pain and pulsatile mass	Angiography, ultrasonography scan	Atheroma	Aneurysmectomy and interposition vein graft between coeliac artery and hepatic artery	Alive and well
12	Present case 2	40	F	Incidental on ultrasonography scan	Angiography, ultrasonography scan	Atheroma	Aneurysmorrhaphy with ePTFE patch	Alive and well

* Patient underwent two procedures; CT, computed tomography; ePTFE, expanded polytetrafluoroethylene

By contrast, before 1985 angiography was employed in 65 per cent of cases, whereas ultrasonography and/or CT scan was performed in only four cases[3].

Forty-three of the 48 patients reported since 1950 by Graham *et al.*[3] underwent surgical treatment; ligation and resection in 35 per cent and vascular reconstruction in 58 per cent. Of those patients reported in the last 5 years (*Table 1*), ligation of the aneurysm was performed in two and vascular reconstruction in ten, including either reimplantation of the coeliac axis to the aorta or an interposition graft with vein or prosthesis. There was only one death in this group (from myocardial infarction), giving a mortality rate (8·3 per cent) comparable to the 9·3 per cent among 43 surgically treated cases before 1985. When ligation of the aneurysm was performed before 1985, two patients died, one from bowel infarction with associated hepatic necrosis[3]. By contrast, the two patients undergoing ligation in the last 5 years both survived. Subtotal pancreatectomy was necessary on one occasion when the aneurysm was found to be adherent to the portal vein[2].

An extensive review of the literature has not revealed another case of coeliac artery aneurysm in a patient with tumoral calcinosis. Although this patient was only 36 years old, there was widespread atherosclerosis with associated aneurysmal changes in the iliac and brachial arteries. It is tempting to suggest a metabolic abnormality as an aetiopathological factor in this patient as there were periods of prolonged calcium/phosphorus imbalance in the form of hyperphosphataemia and later hypercalcaemia after treatment with aluminium hydroxide. We are not aware of any apparent association of Crohn's disease with aneurysms in the splanchnic circulation. Modern radiological techniques have allowed more accurate diagnosis of these aneurysms, leading to successful surgical intervention with a reduction in the risk of rupture.

References

1. Stanley JC, Whitehouse WM Jr. Splanchnic artery aneurysms. In: Rutherford RB, ed. *Vascular Surgery*. Philadelphia: WB Saunders, 1984: 798–813.
2. Wolf RK, Carmichael PA, Clark JH. Coeliac artery aneurysmectomy with pancreatectomy. *J Vasc Surg* 1986; **3**: 817–19.
3. Graham LM, Stanley JC, White WM Jr *et al.* Coeliac artery aneurysms: historic (1745–1949) *versus* contemporary (1950–1984) differences in etiology and clinical importance. *J Vasc Surg* 1985; **2**: 757–64.
4. Flageat J, Buchon R, Sordet D, Schoenenberger P, Metges PJ. Anevrysme de tronc coeliaque. *J Radiol* 1986; **67**: 401–4.
5. Lubbers PR, Goff WB, Volpe RJ, Lichtman D, Gottlieb R. CT diagnosis of coeliac artery aneurysm. *J Comput Assist Tomogr* 1988; **12**: 352–5.
6. Kazui T, Baba M, Komatsu S. Aneurysm of the coeliac artery. *J Cardiovasc Surg* 1988; **29**: 567–9.
7. Melliere D, Becquemin JP, Kassab M, Souadka F. Anevrismes des arteres digestives quelles indications? *Journal des Maladies Vasculaires* 1989; **14**: 206–12.
8. Geelkerken RH, Hajo van Bockel J, de Roos WK, Hermans J. Surgical treatment of intestinal artery aneurysms. *Eur J Vasc Surg* 1990; **4**: 563–7.

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In situ femorodistal bypass: novel technique for angioscope-assisted intraluminal side-branch occlusion and valvulotomy. A preliminary report

To allow and facilitate complete endoluminal vein preparation under angioscopic guidance for in situ *femorodistal bypass grafting, a novel instrument was constructed. In experiments in cadavers we developed the occluder valvulotome, consisting of a modified Mills' valvulotome containing a laterally-ending working channel, a retrograde cutting blade and an advanceable Teflon® tube within the working channel. Using this instrument in combination with commercially available wire coils, we successfully performed five femorocrural* in situ *reconstructions with endoluminal valvulotomy and embolization of a total of ten thigh tributaries. The technique allows angioscope-assisted valvulotomy and simultaneous endoluminal tributary occlusion, making long skin incisions and extensive vein dissection obsolete.*

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Femorocrural *in situ* bypass is an established method of vascular reconstruction for limb salvage and for selected cases of severe claudication[1]. The procedure is technically rather demanding, as vein valves have to be eliminated and main tributaries of the great saphenous vein (GSV) have to be occluded. Various techniques and instruments have been described[2,3].

Despite the good results achieved, the technique has been complicated by uncontrolled, blind valve disruption and tedious localization of tributaries. This may lead to a variety of problems such as vessel wall injury, incomplete valvulotomy, arteriovenous fistula formation, and wound complications due to extensive skin incisions[4]. We have therefore developed a novel technique to facilitate *in situ* vein preparation under angioscopic guidance (*Figure 1*).

Patients and methods

Angioscope

An angiofibrescope (PF 22A, Olympus Incorporated, Zollikon, Switzerland) of outer diameter 2·2 mm, length 120 cm, with a steerable tip was inserted intraluminally into the GSV at the proximal end. In this small-sized, steerable fibrescope no flushing channel is available. Real-time visualization was obtained using a video camera with a monitor (Wolf Incorporated, Knittlingen, Germany).

Occluder valvulotome

A Mills' valvulotome (stainless steel, head diameter 3·2–3·5 mm, length 40 cm) was modified by integrating a working channel, ending laterally in close proximity to the reversed knife. This working channel was bent to about 90° at the tip of the instrument (Mauch Incorporated, Münchenstein, Switzerland). For side-branch occlusion the channel was intubated by a Teflon® (E. I. du Pont, Wilmington, Delaware, USA) tube with an inner diameter of 0·75 mm and a length of 50 cm. The tube was loaded with a wire coil of length 15–25 mm, wire diameter 0·64 mm, and diameter of the coiled coil 2–3 mm (Cook Incorporated, Nottwil, Switzerland). The coil was pushed through the Teflon tube by means of a stainless steel guidewire with a flexible tip of 0·6 mm in diameter and 55 cm in length; the length of the flexible tip was 5 cm. An adjustable handpiece to facilitate handling was integrated at the distal end (*Figure 2*).

Surgical technique

The GSV was mobilized in the area of the distal and proximal anastomoses as described by Leather and Shah[5]. The angioscope was

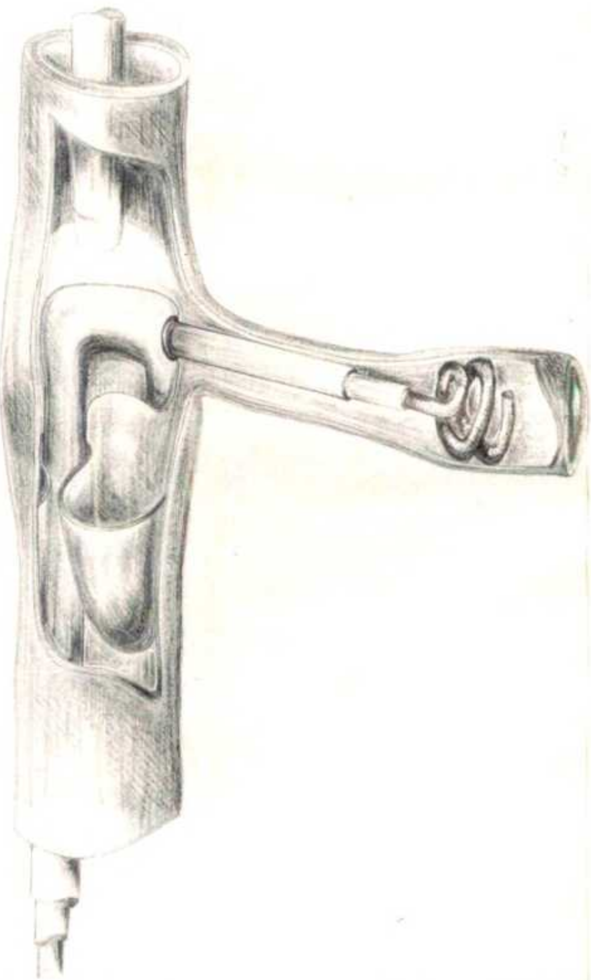

Figure 1 *Intraluminal occlusion of tributaries and valvulotomy. The angioscope is introduced from above and the occluder valvulotome from below. A coil is shown being pushed via the valvulotome into a venous tributary*

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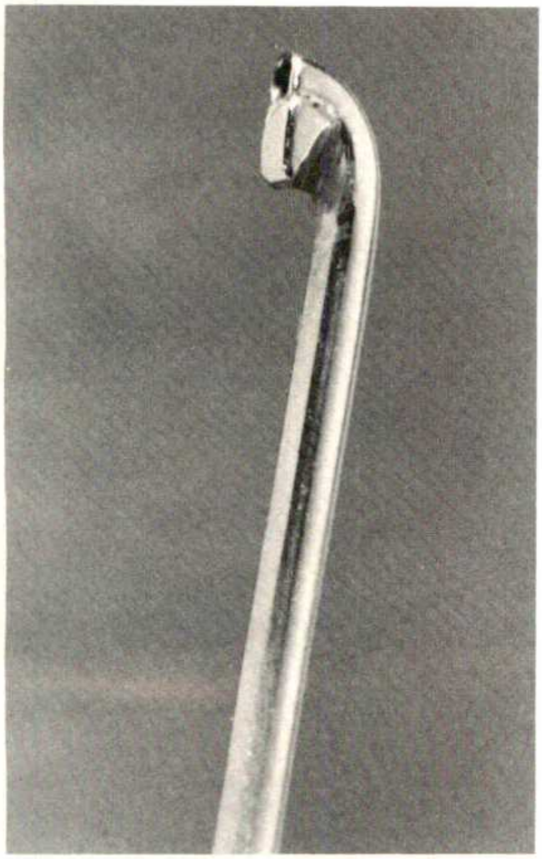

Figure 2 *Occluder valvulotome with a bent working channel and a reversed knife at the tip of the instrument*

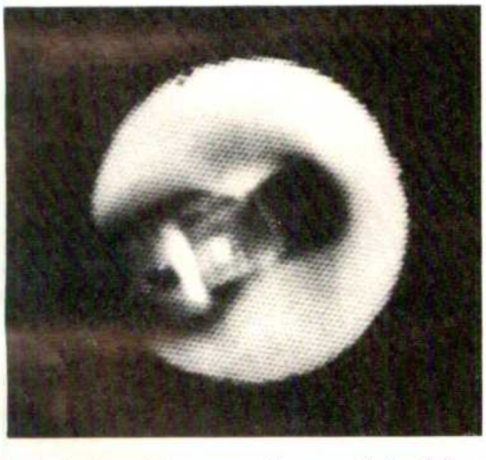

Figure 3 *Intubation of the venous tributary with the Teflon tube. The head of the occluder valvulotome and the black mark on the intubated Teflon tube are visible angioscopically*

introduced intraluminally into the proximal part of the vein. The occluder valvulotome was inserted into the vein through the distal open end. To achieve a clear view within the GSV, a thin venous catheter was inserted proximally or distally following either the angioscope or the valvulotome. The catheter was perfused with Ringer's solution by means of a pneumatic pressure system.

Proceeding from proximal to distal end, the vein valves were cut completely and atraumatically, as described in other reports[6–10]. Simultaneously, before cutting the next pair of valves, a suitable venous tributary in the instrumented segment was located angioscopically. The selected tributary was intubated with the Teflon tube advanced through the working channel of the occluder valvulotome. A black mark on the Teflon tube indicated the depth of intubation (3–5 mm) (*Figure 3*).

To occlude the side-branch, the Teflon tube was loaded with a wire coil. The coil was pushed through the tube into the intubated tributary using the guidewire.

The remaining side-branches were located by the light of the angioscope gleaming through the skin and conventionally clipped via small skin incisions. Proximal and distal anastomoses were peformed using conventional techniques.

Patients

The occluder valvulotome was tested clinically in a selection of five patients requiring femorocrural reconstructions to infrapopliteal arteries (two peroneal, two anterior tibial, one dorsalis pedis). There were two men and three women with an age range of 63–82 years (mean 76 years). All patients suffered from rest pain or gangrene of the foot. In each patient two selected tributaries in the thigh with an inner diameter of between 1·5 and 2·5 mm were embolized using one coil in each tributary. All patients were systemically heparinized with 5000 units heparin after vein preparation and embolization. The embolized tributaries were marked on the skin and the success of the endoluminal occlusion was established by repeated duplex sonography. No protamine was used. After operation the patients were assessed at monthly intervals either by duplex ultrasonography or by angiography. The range of follow-up varied from 2 to 12 months (mean 4 months). All patients received oral anticoagulants for 3–6 months, beginning on the second day after operation.

Results

With the occluder valvulotome it was easy to push the Teflon tube into the selected tributaries under angioscopic guidance. It was often necessary to advance the tube through a closed valve of an afferent side-branch. All of the embolized tributaries occluded after coil insertion. The interval between coil insertion and total side-branch thrombosis ranged from 1 to 10 min after

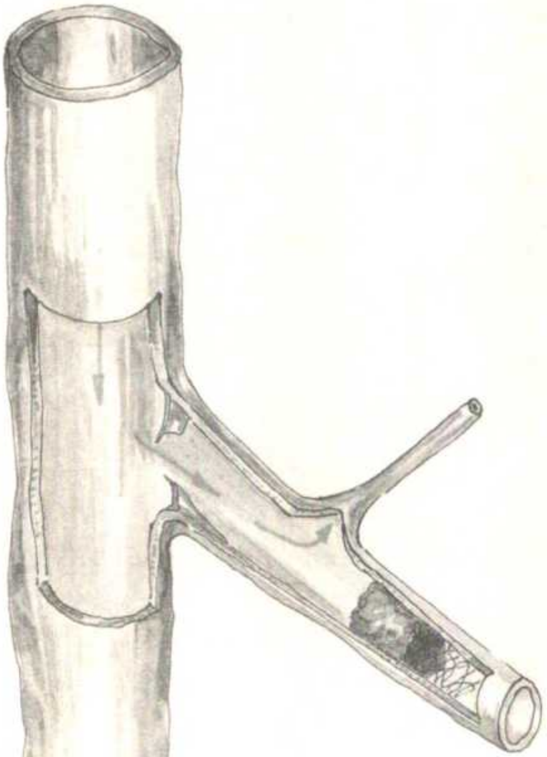

Figure 4 *Residual arteriovenous fistula caused by 2-cm dislocation of a 2-mm coil. Arrows show blood flow down the graft, into the tributary and so to the venous system via a small branch of the tributary exposed by the coil dislocation*

declamping the grafted GSV. The occlusion was durable in nine of ten tributaries during follow-up. In one embolized side-branch a new, clinically irrelevant, arteriovenous fistula was observed on the third day after operation. Angiography demonstrated a 2-cm dislocation of the 2-mm coil, allowing blood flow through a small side-branch of the embolized tributary (*Figure 4*). In the remaining nine embolized tributaries, no coil dislocation was observed. During follow-up all reconstructions remained patent and all patients remained alive without major amputation.

Discussion

In situ bypass grafting has two major technical drawbacks: valve cusps must be eliminated and venous tributaries must be localized and occluded to prevent fistula formation. Achievement of complete and atraumatic valve disruption seems to be a matter of experience rather than relating to the type of instrument. In any event, all 'blind' methods have a definite chance of vein disruption or incomplete valve incision[4].

Now that angiofibrescopes with small diameters have become available, the incision of valve cusps can be performed under continuous vision with good results[6–10]. Unfortunately, the occlusion of venous tributaries has so far required skin incisions and substantial dissection of the GSV. This may lead to wound infections, and such complications after *in situ* and conventional bypass grafting are not uncommon, especially in the thigh[11,12].

To save time and to use the potential advantages of angioscopy, we developed the occluder valvulotome. By using this instrument it is possible to gain access to the venous tributaries from within the lumen of the GSV without skin incisions. The question of occlusive material had to be solved. Pigott *et al.*[13] demonstrated in a dog model the possibility of side-branch occlusion under angioscopic guidance using prolamine (Ethibloc®, Ethicon Incorporated, Worderstedt, Germany). Wire coils with fine Dacron® (E. I. du Pont) hair are in use for radiologically guided embolization in arteries and veins. They are commercially available with very small wire diameters and various lengths and diameters of the coiled coil. We preferred this latter material for the present technique because the extended coil can very easily be advanced through the Teflon tube and positioned within the venous tributary. Kalmann and Sniderman[14] have described a radiologically guided occlusion of an arteriovenous fistula in an *in situ* bypass with two 3-mm wire coils. Coils act only as a nidus for thrombus formation, and thrombosis is needed for side-branch occlusion; it is probably necessary to use different coil sizes for differently sized tributaries to initiate thrombosis.

We believe that the minimal diameter of the coiled coil should measure 3 mm or more to prevent coil dislodgement which can cause residual fistula formation.

The described technique for simultaneous valve disruption and side-branch occlusion under angioscopic guidance should be seen as a preliminary technical report. We think that it is possible to save time and to reduce skin incisions and substantial vein dissection by embolizing tributaries of the GSV, especially in the thigh, but it is obviously necessary to test the putative advantages of the occluder valvulotome in a greater number of patients. The optimal size of the coil required to initiate thrombosis of tributaries of various diameters must also be considered. In the present series we successfully embolized selected side-branches with diameters of 1·5–2·5 mm. Ongoing studies should demonstrate whether this technique is usable as a routine procedure during endoscopically guided vein preparation for *in situ* reconstructions.

References

1. Leather RP, Shah DM, Karmody AM. Infrapopliteal arterial bypass for limb salvage: increased patency and utilization of the saphenous vein used '*in situ*'. *Surgery* 1981; **90**: 1000–8.
2. Enzler MA, Sege D, Rittmann WW. *In situ* Venenbypass: Entwicklung, Technik und Zukunftsperspektiven. *Helv Chir Acta* 1988; **55**: 79–82.
3. Leather RP, Shah DM, Corsan JD, Karmody AM. Instrumental evolution of the valve incision method of *in situ* saphenous vein bypass. *J Vasc Surg* 1984; **1**: 113–23.
4. Levine AW, Bandyk DF, Bonier PH, Towne JB. Lessons learned in adopting the *in situ* saphenous vein bypass. *J Vasc Surg* 1985; **2**: 145–53.
5. Leather RP, Shah DM. Experiences with *in situ* lower extremity saphenous vein bypass procedures. *Surg Annu* 1988; **20**: 257–71.
6. Fleisher AL, Thompson BW, McCowan TC *et al.* Angioscopically monitored saphenous vein valvulotomy. *J Vasc Surg* 1986; **4**: 360–4.
7. Stierli P, Bissat A. Endoskopische Venenpräparation in der peripheren Bypasschirurgie. *Helv Chir Acta* 1990; **57**: 351–4.
8. Stierli P, Bissat A, Streuli HK. Endoscopical vein preparation on peripheral bypass surgery. *Angio Archiv* 1990; **19**: 158–9.
9. Chin AK, Fogarty TJ. Angioscopic preparation for saphenous vein *in situ* bypass grafting. In: Moore WS, Ahn SS, eds. *Endovascular Surgery*. Philadelphia: WB Saunders, 1989: 74–81.
10. Mehigan JT, Schell WW. Angioscopic control of *in situ* saphenous vein arterial bypass. In: Moore WS, Ahn SS, eds. *Endovascular Surgery*. Philadelphia: WB Saunders, 1989: 82–6.
11. Johnson JA, Cogbill TH, Strutt PJ *et al.* Wound complication after infrainguinal bypass: classification, predisposing factors and management. *Arch Surg* 1988; **123**: 859–62.
12. Schwartz ME, Harrington EB, Schanzer H. Wound complications after *in situ* bypass. *J Vasc Surg* 1988; **7**: 802–7.
13. Pigott JP, Donovan DL, Fink JA, Sharp WV. Angioscope-assisted occlusion of veinous tributaries with prolamine in *in situ* femoropopliteal bypass: preliminary results of canine experiments. *J Vasc Surg* 1989; **9**: 704–9.
14. Kalmann PG, Sniderman KW. Salvage of *in situ* femoropopliteal and femorotibial saphenous vein bypass with interventional radiology. *J Vasc Surg* 1988; **7**: 429–32.

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Above-knee prosthetic grafts do not compromise the ipsilateral long saphenous vein

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Prosthetic graft materials are used preferentially by a number of surgeons for above-knee femoropopliteal bypasses. Using B-mode ultrasonography we have assessed the ipsilateral long saphenous vein in patients undergoing such bypasses to determine its suitability for future use in more distal bypasses. A total of 137 above-knee prosthetic grafts were performed over a 10-year period. Of the patients, 74 were available for further assessment. Overall, 97 per cent of veins were suitable for future bypass surgery if required. Above-knee prosthetic bypasses do not appear to jeopardize the ipsilateral long saphenous vein.

The autogenous long saphenous vein is generally regarded as the first choice material for all infrainguinal bypasses[1]. Although all studies to date have shown a significant benefit in terms of patency when using vein as opposed to prosthetic material below the knee, the situation when the distal anastomosis is above the knee is less clear. In a recent study, no significant difference in 5-year patency between vein and prosthetic material was found in this situation[2]. We, therefore, adopt a policy of preferentially using prosthetic materials for above-knee infrainguinal bypasses and thus preserve the long saphenous vein for future, more distal bypass, should this be required.

This policy, however, assumes that the long saphenous vein will still be suitable for use as an arterial conduit at this later date. No previous studies have documented the effect of prosthetic graft implantation on the ipsilateral long saphenous vein. This study was, therefore, designed to assess the suitability of the vein for future bypass surgery after the insertion of a prosthetic above-knee graft.

Patients and methods

Over the 10-year period, January 1980 to December 1989, 137 prosthetic above-knee femoropopliteal bypass grafts were carried out in this centre. Of these, 103 were performed using expanded polytetrafluoroethylene (PTFE) (W. L. Gore and Associates Ltd., Woking, UK) and 34 using denatured human umbilical vein (Meadox UK Ltd., Dunstable, UK). Attempts were made to contact all patients for further review. Further assessment was not possible in 63 patients due to death, major amputation or because they could not be traced. The remaining 74 patients were recalled for duplex scanning of their ipsilateral long saphenous vein. The vein was scanned, with the patient lying on a couch, using a 10 MHz real-time B-mode ultrasonography scanner. Scanning was carried out from the saphenofemoral junction to mid-calf level. The luminal diameter of the vein was measured with screen cursors at the saphenofemoral junction, at the site of the distal anastomosis, and at a point 10 cm below the knee. It was also measured at any other point which appeared narrowed along the course of the vein. Care was taken not to compress the vein with the probe. A diameter $<1{\cdot}5$ mm was deemed to be unsuitable for use as a graft. Vein patency was assessed by squeezing the calf while using pulsed Doppler ultrasonography to confirm flow in the mid-thigh.

Results

Of the 74 patients recalled and scanned, 16 were noted to have had an unsuitable long saphenous vein at the time of their original surgery. These veins were still unsuitable at the time of rescanning. Eleven patients had subsequently had a further, more distal procedure, using their ipsilateral long saphenous vein. Nine of these were still patent and, although two had occluded at 18 and 22 months, both limbs were salvaged. We have concluded, since both grafts were patent for at least 18 months, that none of the 11 veins had been compromised by the initial prosthetic graft implantation. In the other 47 patients,

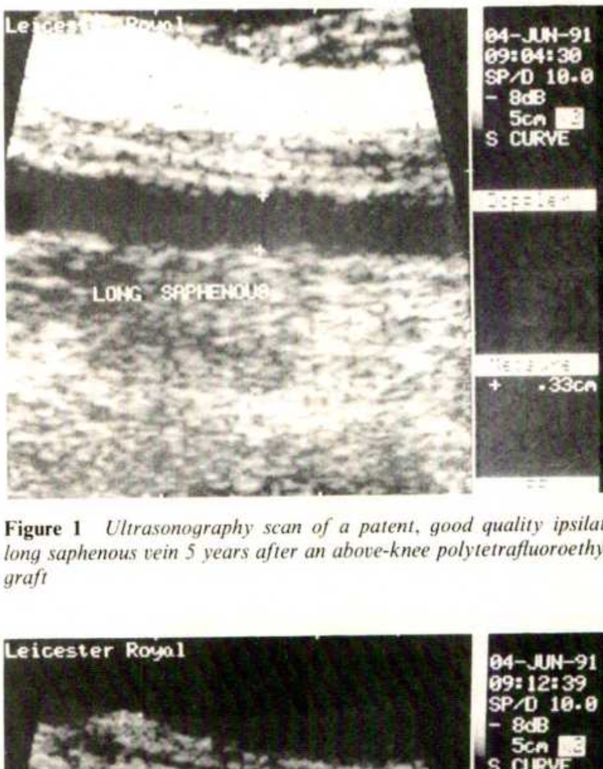

Figure 1 *Ultrasonography scan of a patent, good quality ipsilateral long saphenous vein 5 years after an above-knee polytetrafluoroethylene graft*

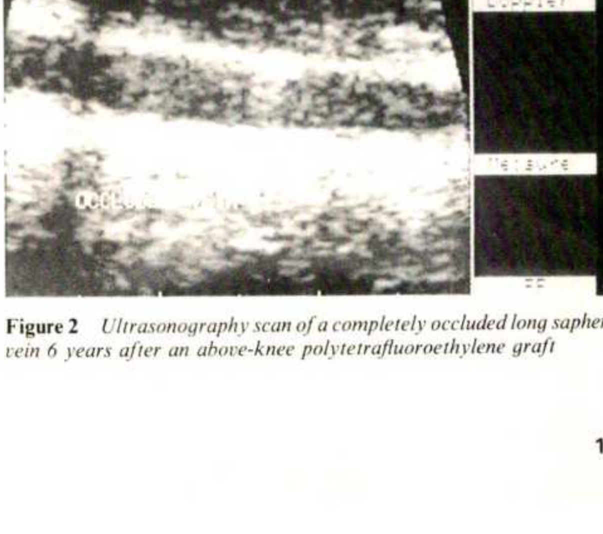

Figure 2 *Ultrasonography scan of a completely occluded long saphenous vein 6 years after an above-knee polytetrafluoroethylene graft*

Based on a presentation to the Vascular Surgical Society, London, UK, 1990

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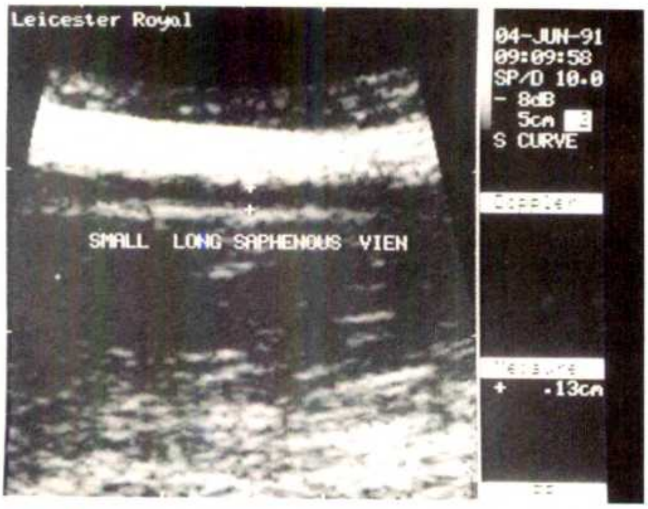

Figure 3 *Ultrasonography scan of a vein narrowed below 1·5 mm at the site of the distal anastomosis of a previous human umbilical vein graft*

43 veins were in good condition (*Figure 1*) and suitable for use as vascular conduits if necessary. One vein was occluded along its length (*Figure 2*) and three veins were narrowed below 1·5 mm in diameter (*Figure 3*). Of these, two were narrowed at a site below the knee and, therefore, away from the site of previous surgery, a situation which probably pertained at the time of the initial surgery, although this could not be confirmed. The other vein was narrowed to 0·7 mm in the region of the previous distal skin incision. It appeared to have been incorporated in the resulting scar tissue. From these figures it appears that, at worst, 54 (93 per cent) of 58 veins remain suitable after above-knee prosthetic graft implantation. If the two veins narrowed only below the knee are grouped with those unsuitable at the time of initial surgery, this figure rises to 97 per cent.

Discussion

Although autogenous saphenous vein appears to provide the best conduit for infrainguinal bypass at the present time, it may be unsuitable or unavailable in many patients[3]. In these patients, prosthetic materials offer an alternative to amputation. Furthermore, some surgeons use prosthetic materials preferentially in above-knee femoropopliteal bypasses for a variety of reasons[4,5]. Patency rates for these grafts in the above-knee position have been reported as good by a number of authors. In a recent study, Gupta *et al.*[6] reported a 3-year graft patency rate of 76 per cent for PTFE in the above-knee position. Indeed, even in below-knee femoropopliteal bypasses they achieved a 62 per cent 3-year patency rate. Because of these reports and our own experience[2], we also adopt a policy of preferentially using PTFE for above-knee femoropopliteal bypass. One of the reasons put forward for adopting this policy is that it saves the long saphenous vein for use in future, more distal bypasses should they become necessary. Obviously, if this reason is to be substantiated it needs to be shown that the vein is still usable at this later date.

Assessment of the long saphenous vein by venography is only partially successful in picking up veins unsuitable for use as vascular conduits[7,8]. At the present time many centres now use real-time B-mode ultrasonography for this purpose and to map the vein before operation[9]. More recently, colour assisted duplex sonography has been used, especially in follow-up[10]. We have used the B-mode scanner. It is still not totally clear what minimum diameter of vein is suitable for infrainguinal bypass, but in our experience veins below 1·5 mm perform poorly, even in the *in situ* procedure. For this reason this cut-off point was chosen in assigning a vein unsuitable in this study. The results indicate that prosthetic above-knee graft implantation does not adversely affect the ipsilateral long saphenous vein in the vast majority of patients. It also confirms that some patients do subsequently require a below-knee or more distal graft and that the vein works well in this situation. In those veins deemed not suitable for subsequent use as grafts, damage caused directly by the initial surgery was only fully attributable in two cases. In both cases the distal incision was in close proximity to the saphenous vein. In one case the vein became occluded and in the other it became narrowed, seemingly due to incorporation in the scar tissue. This may well have been avoided if the vein had been mapped out by ultrasonography before the prosthetic graft insertion. In this way the incision could have been kept as far away as possible from the long saphenous vein. We now routinely mark the vein before operation, even if performing a prosthetic bypass. In conclusion, if a policy of preferentially using prosthetic materials for above-knee femoropopliteal bypasses is adopted, the long saphenous vein is generally preserved for future use if it is required.

References

1. Michaels JA. Choice of material for above-knee femoropopliteal bypass graft. *Br J Surg* 1989; **76**: 7–14.
2. Budd JS, Brennan J, Beard JD, Warren H, Burton PR, Bell PRF. Infrainguinal bypass surgery: factors determining late graft patency. *Br J Surg* 1990; **77**: 1382–7.
3. Veith FJ, Gupta SK, Ascer E *et al.* Six year prospective multicentre randomized comparison of autologous saphenous vein and expanded polytetrafluoroethylene grafts in infrainguinal arterial reconstructions. *J Vasc Surg* 1986; **3**: 104–14.
4. Quinones-Baldrich WJ, Martin-Paredero V, Baker JD, Busuttil RW, Machleder HI, Moore WS. Polytetrafluoroethylene grafts as the first choice arterial substitute in femoropopliteal revascularization. *Arch Surg* 1984; **119**: 1238–47.
5. Haimov H, Giron F, Jacobson JH. The expanded polytetrafluoroethylene graft – three years experience with 362 grafts. *Arch Surg* 1979; **114**: 673–7.
6. Gupta SK, Veith FJ, Kram HB, Wengerter KR. Prospective, randomized comparison of ringed and non-ringed polytetrafluoroethylene femoropopliteal bypass grafts: a preliminary report. *J Vasc Surg* 1991; **13**: 162–72.
7. Veith FJ, Moss CM, Sprayregen S, Montefusco C. Preoperative saphenous venography in arterial reconstructive surgery of the lower extremity. *Surgery* 1979; **85**: 253–6.
8. Mosley JG, Manhire AR, Raphael M, Marston JAP. An assessment of long saphenous venography to evaluate the saphenous vein for femoropopliteal bypass. *Br J Surg* 1983; **70**: 673–4.
9. McShane MD, Field J, Smallwood J, Chant ADB. Early experience with B mode ultrasound mapping of the long saphenous vein prior to femorodistal bypass. *Ann R Coll Surg Engl* 1988; **70**: 147–9.
10. Polak JF, Donaldson MC, Dobkin GR, Mannick JA, O'Leary DH. Early detection of saphenous vein arterial bypass graft stenosis by colour assisted Duplex sonography: a prospective study. *AJR* 1990; **154**: 857–61.

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Effect of low molecular weight heparin on intimal hyperplasia

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Intimal hyperplasia is a significant cause of vascular graft failure. To investigate the potential uses of low molecular weight heparins (LMWHs) as prophylactic agents against graft thrombosis in humans, the anti-proliferative effects of a regimen of subcutaneous LMWH have been studied in an experimental model. Aortic intimal hyperplasia was created in 30 New Zealand White rabbits by endothelial denudation using an embolectomy balloon catheter technique. Three groups of ten animals were randomized to act as controls or to be treated with subcutaneous LMWH once or twice daily for 4 weeks. At 4 weeks all animals were killed and the aortas were harvested for analysis. The degree of intimal hyperplasia was measured using a computerized image analysis system and was expressed as an intimal:medial area ratio and also as percentage luminal reduction. A 60 per cent reduction in the degree of intimal hyperplasia was seen following treatment with LMWH. Heparin-treated animals had considerably less luminal reduction (daily LMWH 8 per cent and twice-daily LMWH 10 per cent) compared with untreated controls (26 per cent) ($P<0{\cdot}001$). *There was a similar difference seen in the intima:media area ratios, daily LMWH 0·38, and twice-daily LMWH 0·44,* versus *controls, 1·11* ($P<0{\cdot}001$). *In an experimental model, subcutaneous LMWH therapy effectively inhibits intimal hyperplasia.*

Following its introduction by Kunlin[1] in 1948, femoropopliteal arterial bypass grafting has proved successful in relieving the symptoms of claudication and in salvaging critically ischaemic limbs. The success of this form of surgery depends on sustained graft patency. Reported patency rates vary from 40 to 90 per cent after 1 year. Even the results using autologous vein as a conduit can be disappointing, with up to 24 per cent of grafts failing in the first year[2].

One of the most important causes of vascular graft failure within the first year of surgery is intimal hyperplasia[3]. This process of structural change with progressive luminal obliteration caused by a thickening of the vessel wall between the internal elastic lamina and the endothelium appears to be a response to injury[4]. The cellular processes resulting in intimal hyperplasia involve the migration and proliferation of smooth muscle cells from the vessel media[5]. Clinical and pathological studies have shown that the development of intimal hyperplasia at the anastomotic sites of venous and prosthetic grafts is the most important factor affecting the outcome of these grafts[6–8]. If this process could be inhibited then the results of vascular bypass surgery might be improved.

In 1977, Clowes and Karnovsky demonstrated that heparin possesses anti-proliferative effects capable of inhibiting intimal hyperplasia following deliberate arterial injury[9]. Further workers have confirmed this effect *in vivo*[10] and others have demonstrated the anti-proliferative effects of heparin on smooth muscle cells *in vitro*[11]. Conventional heparin needs to be administered by continuous intravenous infusion or by regular subcutaneous injections twice or three times a day. Furthermore, it is associated with side-effects such as haemorrhage, thrombocytopenia and osteoporosis. For these reasons conventional heparin is unlikely to be accepted as a long-term therapy in vascular surgery. The development of low molecular weight heparins (LMWHs), with longer half-lives than conventional heparin, has provided an effective and acceptable method of treating patients by once-daily subcutaneous injection. If the new generation of LMWHs displays the anti-proliferative effects of conventional heparin, then this form of therapy may have great clinical relevance. This study presents the experimental approach used to evaluate the effects of subcutaneous LMWH therapy on intimal hyperplasia.

Materials and methods

Thirty male New Zealand White rabbits underwent endothelial denudation of the infrarenal aorta using a balloon catheter. Animals were assigned to either a control group ($n=10$) or a treatment group ($n=20$). Those animals in the treatment group were randomized to receive either once-daily or twice-daily regimens of subcutaneous LMWH for the duration of the study (ten animals in each group). Animals survived for 4 weeks, after which time they were killed and the aortas were harvested for analysis of intimal hyperplasia.

Operative technique

Animals were anaesthetized using a regimen of subcutaneous Hypnorm (Janssen Pharmaceutical Ltd., Oxford, UK) and intravenous midazolam. The right femoral artery was displayed and a 4 Fr embolectomy catheter was introduced via an arteriotomy for a distance of 15 cm from the point of insertion. This distance had previously been shown to place the tip of the catheter below the renal arteries. The balloon was inflated with 0·4 ml saline and the catheter was withdrawn. This process was repeated five times and with each passage the catheter was rotated to ensure circumferential endothelial removal. The femoral artery was ligated and the wounds were closed in layers.

Protocol

Animals were housed individually and had free access to water and a standard pelleted diet. They were fed fresh hay daily. All animals received a subcutaneous injection of 60 anti-factor Xa units LMWH per kg body-weight on induction of anaesthesia. Animals in the treatment groups continued with this dose of heparin once ($n=10$) or twice ($n=10$) a day. Preliminary pharmacokinetic studies in ten rabbits had shown that a single dose of 60 anti-Xa units LMWH per kg body-weight gave measurable levels of heparin within an acceptable therapeutic range for anti-coagulation over 12 h (*Figure 1*). On this basis this dose of heparin was given either once or twice daily. The

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Paper based on a presentation given at the meeting of the Surgical Research Society held in Southampton, UK in July 1990

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LMWH was Fragmin®, 10 000 anti-Xa units/ml (Heparin Fragment Kabi 2165, Kabi Vitrum, Stockholm, Sweden). It was manufactured from porcine intestinal mucosal unfractionated heparin, by controlled nitrous acid degradation. It has a mean molecular weight of 4000–5000 and a specific activity of 165 units/mg in anti-Xa assay and 40 units/mg in activated partial thromboplastin time (APTT) assay, giving an anti-Xa:APTT ratio of 4:1.

Preparation of aortas

Under deep anaesthesia a median sternotomy was performed and the descending thoracic aorta was cannulated. A solution of 10 per cent formaldehyde was then infused at a pressure of 100 mmHg for 10 min to fix the vasculature *in situ*. The abdominal aorta was then displayed and a 5-mm section removed at a distance of 2 cm below the left renal artery and further fixed in formaldehyde.

Sections were prepared by standard paraffin techniques; 4 μm thick sections were cut, dewaxed in xylene, hydrated, and stained with haematoxylin and eosin. Three sections from each aortic preparation were mounted and used for morphometric analysis of intimal hyperplasia.

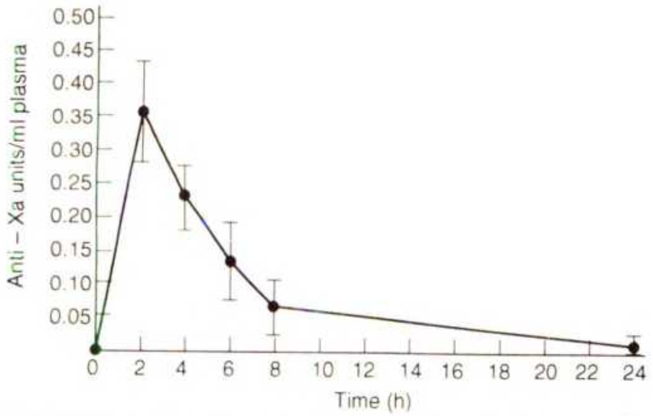

Figure 1 *Twenty-four-hour heparin levels following a single subcutaneous injection of 60 anti-Xa units low molecular weight heparin per kg body-weight (mean values from ten animals)*

Morphometric analysis

This was performed using an interactive image analysis system (Kontron Instruments, Watford, UK). Each histological preparation was placed on a microscope to which a camera was attached. The captured image was fed to the computer system and a digitized image was reproduced on a computer monitor. Using a digitizing pad the outline of the constituent parts of the aortic sections (external elastic lamina, internal elastic lamina and luminal perimeter) could be defined and from this information the computer program, written especially for this purpose, calculated vessel diameter and medial, intimal and luminal areas. Morphometric analysis of intimal hyperplasia was measured on three specimens and the mean value was taken. The technique is highly reproducible; the coefficient of variation for intraobserver error is less than 4 per cent.

Intimal hyperplasia was expressed as an intima:media ratio and as percentage luminal reduction. In normal vessels the intima comprises a one-cell-thick endothelium. The vessel lumen therefore approximates to the area bounded by the internal elastic lamina. In vessels demonstrating intimal thickening, the lumen becomes defined by the intimal surface. The difference between these two measurements in the affected vessels gives an indication of luminal area reduction caused by intimal thickening.

Statistical analysis

Data were analysed using the Mann–Whitney *U* test. Significance was accepted at the 5 per cent level.

Results

There were no animal deaths. Two animals sustained ischaemic ulceration of the ipsilateral paw following femoral artery ligation. This was superficial, did not affect animal well-being, and healed completely within 2 weeks.

Typical histological findings are shown in *Figures 2* and *3*. Marked intimal thickening caused by smooth muscle cell proliferation was seen in the subendothelial layer in control animals (*Figure 2*). The degree of intimal hyperplasia in animals receiving LMWH appeared less (*Figure 3*).

The results of the morphometric analysis quantifying these findings are shown in *Table 1*. The vessels were of consistent

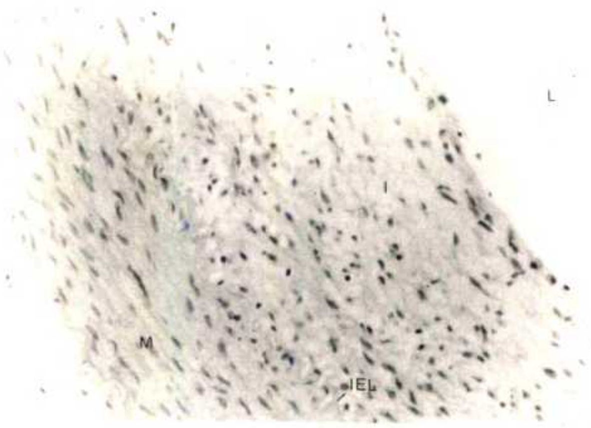

Figure 2 *Transverse section of rabbit aorta (control) stained with haematoxylin and eosin, showing lumen (L), thick intimal layer (I), internal elastic lamina (IEL) and media (M) (original magnification ×100)*

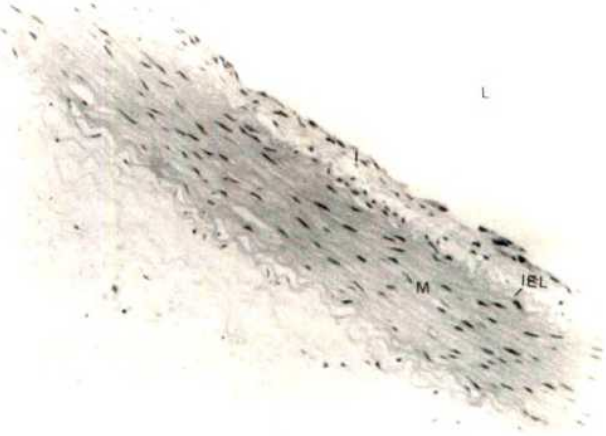

Figure 3 *Transverse section of rabbit aorta (heparin group) stained with haematoxylin and eosin, showing lumen (L), thick intimal layer (I), internal elastic lamina (IEL) and media (M) (original magnification ×100)*

Table 1 *Morphometric analysis of intimal hyperplasia*

	Vessel diameter (mm)	Medial area (mm²)	Intima:media area ratio	Percentage luminal reduction
Control	2·71(0·31)	0·65(0·15)	1·11 (0·96–1·17)	26 (18–31)
Daily LMWH	2·81(0·14)	0·69(0·13)	0·38 (0·24–0·61)	8 (5–12)
Twice-daily LMWH	2·65(0·20)	0·59(0·11)	0·44 (0·32–0·61)	10 (6–11)

Values for diameter and medial area are mean(s.d.); values for intimal hyperplasia are medians with interquartile range in parentheses. LMWH, low molecular weight heparin. Controls *versus* LMWH, $P < 0·001$; daily LMWH *versus* twice-daily LMWH, $P > 0·05$ (Mann–Whitney *U* test) size in all groups and there were no significant differences in the medial areas of the vessels. Intimal hyperplasia has been expressed as the ratio of intimal:medial area, and as the percentage luminal reduction that results from the occlusive process. The former allows for minor changes within the vessel sizes and the latter equates intimal hyperplasia with a real effect on luminal size. There was a statistically significant reduction in the degree of intimal hyperplasia seen in those animals receiving LMWH when compared with controls ($P<0{\cdot}001$). This difference was also seen when analysing the intimal:medial area ratios. Heparin therapy inhibited intimal hyperplasia by an order of 60 per cent. There were no differences between the two heparin regimens. There were no known complications from heparin therapy.

Discussion

Approximately 65 per cent of femoropopliteal graft failures occur in the first 12 months, mostly as a result of the consequences of intimal hyperplasia[2]. To improve results it has been suggested that graft surveillance should be performed. While this is effective, it is costly and time-consuming. Prevention of intimal hyperplasia may be a better option. The response to injury hypothesis for intimal hyperplasia identified a key role for the involvement of platelets[12]. As a result, methods of improving graft patency using anti-platelet therapy have been extensively reported. Anti-platelet therapy effectively reduces graft thrombogenicity[13] and has been shown to improve the outcome for prosthetic grafts[14]. However, the beneficial effects of anti-platelet therapy on venous conduits is still unconfirmed[15] and experimental work has sometimes failed to show an inhibitory effect on intimal hyperplasia with these agents[16].

Heparin inhibits smooth muscle cell proliferation and thus has a direct effect on the cells responsible for intimal hyperplasia. It may therefore have the potential to be an effective agent for improving vascular graft patency through its anti-proliferative and anti-thrombotic effects. This study has shown that a daily subcutaneous injection of LMWH for 1 month effectively inhibits intimal hyperplasia by the order of 60 per cent compared with untreated controls. Previous studies using a carotid artery model have shown that by 4 weeks intimal hyperplasia is maximal and endothelial regeneration is nearly complete[17]. Under such circumstances a short course of therapy may be effective in preventing the proliferative response. Although what would happen following cessation of therapy is unknown, present findings, together with our own observations of endothelial recovery in this model, suggest that a prolonged course of LMWH therapy may be unnecessary.

Pomposelli and co-workers showed that an increase in wall tension due to haemodynamic stresses at anastomoses results in intimal hyperplasia[18]. Previously presented work from our own laboratories showed that stimulated smooth muscle cells express gene activation for the messenger RNA signal for the production of endogenous platelet-derived growth factor. Smooth muscle cells therefore demonstrate an autocrine mechanism whereby they can control their own proliferation, independent of platelets[19]. These two observations may explain why anti-platelet therapy appears to be less effective in preventing late graft occlusion in venous grafts. Heparin, by having an inhibitory effect at the cellular level, has the potential to inhibit intimal hyperplasia in both vein and prosthetic grafts and thus improve patency.

In addition to its anti-proliferative effects, the anti-thrombotic effects of heparin, together with the ability of LMWHs to inhibit platelet aggregation[20], may be of benefit. Recently, Pfisterer and co-authors showed that anti-coagulation with warfarin was as effective as anti-platelet therapy in improving the patency of coronary artery bypasses[21], although warfarin was associated with significantly more haemorrhagic side-effects.

LMWH has provided an effective and practical means of administering anti-thrombotic therapy. This study has shown that such an agent has an inhibitory effect on intimal hyperplasia in an experimental model. Whether or not this effect can confer clinical benefit remains to be shown.

References

1. Kunlin J. Le traitement de l'arterite obliterante par la greffe veineuse. *Arch Mal Coeur* 1949; **42**: 371.
2. Harris PL, How TV, Jones DR. Prospectively randomised clinical trial to compare *in situ* and reversed saphenous grafts for femoropopliteal bypass. *Br J Surg* 1986; **74**: 252–5.
3. Imparato AM, Bracco A, Kim GE, Zeff R. Intimal and neointimal fibrous proliferation causing failure of arterial reconstructions. *Surgery* 1972; **72**: 1007–17.
4. Clowes AW. Pathobiology of arterial healing. In: Strandness DE, Didisheim P, Clowes AW, Watson JT, eds. *Vascular Diseases – Current Research and Clinical Applications.* New York: Grune and Stratton, 1987: 351–61.
5. Schloss G, Schumacker HB. Studies in vascular repair: IV. The use of free vascular transplants for bridging arterial defects: an historical review with particular reference to histological observations. *Yale J Biol Med* 1950; **22**: 273–90.
6. Szilagyi DE, Elliott JP, Hageman JH, Smith RF, Dall'olmo CA. Biological fate of autogenous vein implants as arterial substitutes. Clinical angiographic and histologic observations in femoro-popliteal operations for atherosclerosis. *Ann Surg* 1973; **178**: 232–44.
7. Sottiurai VS, Yao JST, Flinn WR, Batson RC. Intimal hyperplasia and neointima: an ultrastructural analysis of thrombosed grafts in humans. *Surgery* 1983; **93**: 809–17.
8. DeWeese JA, Green RM. Anastomotic neointimal fibrous hyperplasia. In: Bernhard VM, Towne JB, eds. *Complications in Vascular Surgery.* New York: Grune and Stratton, 1980: 153–65.
9. Clowes AW, Karnovsky MJ. Suppression by heparin of smooth muscle cell proliferation in injured arteries. *Nature (Lond)* 1977; **265**: 625–6.
10. Guyton JR, Rosenberg RD, Clowes AW, Karnovsky MJ. Inhibition of rat arterial smooth muscle cell proliferation by heparin. *In vivo* studies with anticoagulant and non anticoagulant heparin. *Circ Res* 1980; **46**: 625–33.
11. Hoover RL, Rosenberg RD, Haering W, Karnovsky MJ. Inhibition of rat arterial smooth muscle cell proliferation by heparin. II. *In vitro* studies. *Circ Res* 1980; **47**: 578–83.
12. Ross R, Glomsett J, Kariya B, Harker LA. A platelet dependent serum factor that stimulates the proliferation of arterial smooth muscle cells *in vitro*. *Proc Natl Acad Sci USA* 1974; **71**: 1207–10.
13. Harker LA, Slichter SJ, Sauvage LR. Platelet consumption by arterial prosthesis: the effects of endothelialization and pharmacologic inhibition of platelet function. *Ann Surg* 1977; **186**: 594–601.
14. Clyne CAC, Archer TJ, Atuhaire LK, Chant ADB, Webster JHH. Random control trial of a short course of aspirin and dipyridamole (Persantin) for femorodistal grafts. *Br J Surg* 1987; **74**: 246–8.
15. McCollum CN. Does platelet inhibitory therapy improve vein bypass patency. In: Greenhalgh RM, Jamieson CW, Nicolaides AN, eds. *Limb Salvage and Amputation for Vascular Disease.* London: WB Saunders, 1988: 307–18.
16. Murday AJ, Gershlick AH, Syndercombe-Court D, Mills PG, Lewis CT. Intimal thickening in autologous vein grafts in rabbits: influence of aspirin and dipyridamole. *Thorax* 1984; **39**: 457–61.
17. Kohler TR, Kirkman T, Clowes AW. Effect of heparin on adaptation of vein grafts to arterial circulation. *Arteriosclerosis* 1989; **9**: 523–8.
18. Pomposelli F, Schoen F, Cohen R *et al.* Conformational stress and anastomotic hyperplasia. *J Vasc Surg* 1984; **1**: 525.
19. Parker CJ, Kanthou C, Stroobant P *et al.* Atheroma – a new hypothesis. *Br J Surg* 1987; **74**: 526.
20. Westwick J, Scully MF, Poll C, Kakkar VV. Comparison of the effects of low molecular weight heparin and unfractionated heparin on activation of human platelets *in vitro*. *Thromb Res* 1986; **42**: 435–47.
21. Pfisterer M, Jockers G, Regenass S *et al.* Trial of low dose aspirin plus dipyridamole *versus* anticoagulants for prevention of aortocoronary vein graft occlusion. *Lancet* 1989; **ii**: 1–7.

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Quantitative measure of small vessel anastomotic contour using corrosion resin cast models: an aid to surgical training

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A surgeon who had not previously carried out a small vessel anastomosis performed 20 consecutive anastomoses between human long saphenous vein and the left anterior descending artery of a pig's heart. Corrosion resin cast models were made of the anastomoses and subjected to a quantitative analysis of the anastomotic contour. A trend of improvement in contour parameters was found with increasing experience. This model may be useful for surgeons in training.

Different surgeons vary in their innate skill at performing surgical techniques[1,2], and formal training in suturing techniques should be established as part of the training of all surgeons[2]. The aim of this study was to develop a technique to quantify a vascular anastomotic contour and to illustrate its use as a potential training tool for performing small vessel anastomoses.

Materials and methods

Twenty fresh pigs' hearts and 20 segments of human long saphenous vein were used.

A junior surgeon who had not previously performed small vessel anastomoses was supervised in anastomosing a segment of long saphenous vein to the left anterior descending artery (mean diameter 1 mm) of a pig's heart (end-to-side) using 6/0 polypropylene. Over the course of 1 month the surgeon performed a total of 20 such anastomoses.

The external appearance of an anastomosis is not a reliable indicator of the internal configuration[3]. One method of studying the internal configuration is by making accurate anatomical models of the anastomosis by the use of resin. The resin in this study, Biodur E 20 (Biodur, Heidelberg, Germany), is reported to have the advantageous properties of epoxy resin: high firmness, good curing in the presence of biological tissue, and minimal shrinkage (less than 2 per cent), together with good flow properties on wet surfaces such as the walls of blood vessels[4].

Corrosion resin cast models were made of all the anastomoses using Biodur E 20 injected at a pressure of 100 mmHg. Resin cast models (*Figure 1*) were obtained after maceration with 40 per cent potassium hydroxide.

The junior surgeon was aware of the results of the model analyses as they were completed and modified his technique accordingly.

Measurement

An anastomometer was developed by adapting a digital readout lens meter (accurate to 0·01 mm) to make quantitative measurements of the anastomotic contour. Readings were taken from three regions: the preanastomotic region, the anastomotic region and the postanastomotic region. The lengths of the preanastomotic and postanastomotic regions were the same as the length of the anastomosis. Measurements were made of the diameter of the cross-sectional plane at five points in each region. Three readings of diameter (d_1–d_3) were taken for each cross-sectional plane at three different angles about the midpoint, making a total of 45 measurements from each anastomosis. From these measurements, two parameters of anastomotic contour were calculated; the mean anastomotic narrowing (MAN) and the distortion factor (DF), which were calculated as follows.

$$\mathrm{MAN} = \frac{\mathrm{MA}_{\mathrm{ca}} - \mathrm{MA}_{\mathrm{an}}}{\mathrm{MA}_{\mathrm{ca}}} \times 100\%$$

where $\mathrm{MA}_{\mathrm{ca}}$ is the mean cross-sectional area of the coronary artery, taken as the mean of the cross-sectional areas of the preanastomotic and postanastomotic regions, and $\mathrm{MA}_{\mathrm{an}}$ is the mean cross-sectional area of the coronary artery along the anastomotic region.

MAN is a measure of the overall narrowing of the coronary artery along the length of the anastomosis; the more positive its value the greater the overall narrowing.

$$\mathrm{DF} = \frac{\mathrm{MD}_{\mathrm{v,ca}} - \mathrm{MD}_{\mathrm{v,an}}}{\mathrm{MD}_{\mathrm{v,ca}}} \times 100\%$$

where $\mathrm{MD}_{\mathrm{v,ca}}$ is the mean variation in the cross-sectional diameters at each of the five cross-sectional planes of measurement of the preanastomotic and postanastomotic regions, and $\mathrm{MD}_{\mathrm{v,an}}$ is the mean variation in the cross-sectional diameters at each of the five cross-sectional planes of measurement of the anastomotic region.

The distortion factor is a measure of any local asymmetry in the cross-sectional area of the coronary artery at the site of the anastomosis; the more negative its value, the greater the asymmetry caused by the anastomosis.

An ideal anastomotic contour would have MAN and DF values of zero.

Results

These are shown in graphic form in *Figures 2* and *3*. For comparison, a series of models made by two more experienced surgeons produced values of MAN between 0 and 20 per cent and DF between 0 and −20 per cent. The solitary model (number 19) with a negative MAN may represent anatomical variation of the coronary artery or may be a consequence of the limitations of the degree of accuracy of the technique.

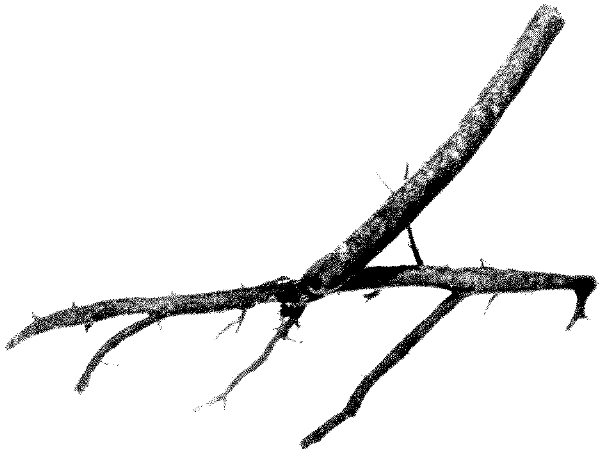

Figure 1 *Example of a corrosion resin cast model of a saphenous vein–coronary artery anastomosis*

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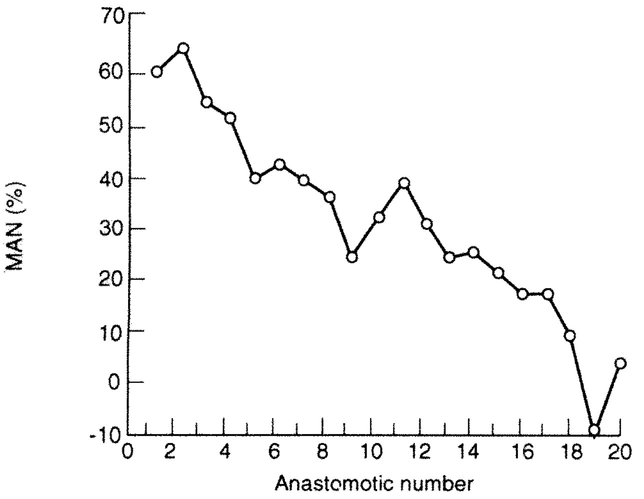

Figure 2 *Variation of mean anastomotic narrowing (MAN) with the number of anastomoses performed*

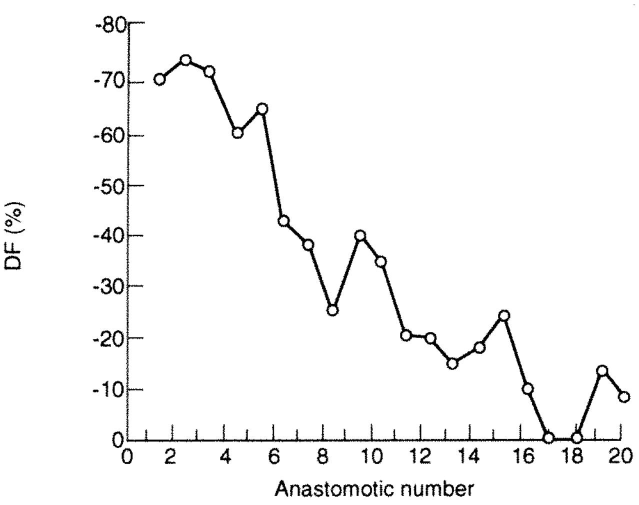

Figure 3 *Variation of distortion factor (DF) with the number of anastomoses performed*

Discussion

The principal aims in performing a vascular anastomosis are to ensure immediate patency and to maximize the chances of it remaining patent in the long term. The latter may be partly dependent on the contour of the vascular anastomosis.

A number of reports[3,5,6] have examined the patency of small vessel anastomoses using different techniques and concluded that the technical skill of the surgeon was the most important factor.

The immediate or short-term patency of a graft is a very gross assessment of quality of anastomosis. An immediately non-patent graft represents a major error of technique, but more subtle differences in anastomotic contour may be important in determining long-term patency. Young *et al.*[3], using a similar method to that described in this report, made purely qualitative observations on the presence of 'purse-stringing', kinking, corner narrowing and notching deformities. Shioi[7] attempted a quantitative assessment of the same models, but the estimation of the degree of stenosis was a subjective measurement.

The two parameters used in this study, MAN and DF, provide a quantitative measure of narrowing or other distortion of the anastomotic site. The general trend of these values was to approach the ideal anastomotic contour with MAN and DF values of zero. This was achieved with increasing experience in a particular technique and by modifying technique in the light of quantitative assessment of previous resin models.

This model may be suitable for training purposes for small vessel anastomoses.

References

1. Seki S. Suturing techniques of individual surgeons: differences in accuracy and mechanics. *Jpn J Surg* 1989; **4**: 424–31.
2. Seki S. Techniques for better suturing. *Br J Surg* 1988; **75**: 1181–4.
3. Young JN, MacMillan JC, May IA, Iverson LIG, Ecker RR. Internal configuration of saphenous–coronary anastomoses as studied by the cast-injection technique. *J Thorac Cardiovasc Surg* 1975; **2**: 179–85.
4. Tiedemann K, von Hagens G. The technique of heart plastination. *Anat Rec* 1982; **204**: 295–9.
5. Guity A, Young PH, Fischer VW. In search of the 'perfect' anastomosis. *Microsurgery* 1990; **11**: 5–11.
6. Hayhurst JW, O'Brien BM. An experimental study of microvascular technique, patency rates and related factors. *Br J Plast Surg* 1975; **28**: 128–32.
7. Shioi K. A study of sequential anastomoses of aortocoronary bypass surgery: internal configurations by the casting injection technique. *Nagoya J Med Sci* 1984; **46**: 19–26.

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Effect of weight on claudication distance

Conservative measures to improve claudication distance include advice on smoking, exercise, diet and weight reduction. Although the effects of smoking, exercise and diet are established, the effect of weight is less clear. The aim of this study was to investigate the effect of carrying extra weight on the maximum walking distance in stable claudicants. Twenty stable claudicants were exercised on a treadmill (3·5 km/h, 0° slope) carrying 0, 2·5, 5, 7·5 and 10 kg weights in randomized sequence. Maximum claudication distance and ankle:brachial pressure indices were recorded. Patients were categorized into mild or severe claudicants depending on their ability to walk 200 m. A response index (RI) was calculated as the reduction in claudication distance per kilogram load; $RI=[CD_0-CD_{10}]/10$ *m/kg, where* CD_0 *and* CD_{10} *represent claudication distance with 0 and 10 kg weights, respectively. Claudication distance was significantly reduced in subjects carrying 5 kg or more* ($P<0{\cdot}01$). *A linear relationship was demonstrated between the mean claudication distance and the load carried* ($r=0{\cdot}98$, $P<0{\cdot}01$) *with a mean response index of 10·2 m/kg. The mean(s.e.m.) RI in mild claudicants (25·9(9·5) m/kg) was greater than the value observed in the severe claudicants (3·3(0·8) m/kg;* $P<0{\cdot}01$, *Mann–Whitney* U *test). This study demonstrates that weight adversely affects claudication distance and suggests that weight reduction may deserve greater emphasis in the management of some patients with intermittent claudication.*

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The management of stable claudication remains controversial, but most vascular surgeons would recommend conservative treatment in the form of regular exercise and cessation of smoking[1], with balloon angioplasty or surgical intervention reserved for those with chronic incapacitating or progressive disease[2,3].

Although obesity has been shown to be a predictor of the incidence of and mortality from coronary artery atherosclerosis[4,5], the effect of weight on patients with peripheral atherosclerosis is unknown. Theoretically the carrying of excess weight should shorten claudication distance, but clinical evidence in support of this hypothesis is lacking[6]. In any long-term prospective study it would be difficult or even impossible to clarify the association between weight and claudication because of the confounding effect of changing risk factors, especially smoking.

This study was designed to investigate the effect of increasing weight on the maximum walking distance in stable claudicants. By performing all measurements during the same hospital visit, the variability associated with alteration in other risk factors was minimized.

Patients and methods

Twenty consecutive patients with stable claudication were recruited from the vascular outpatient clinic (male:female ratio 14:6, age range 42–78 years). Patients with critical ischaemia or evidence of cardiorespiratory insufficiency were excluded from the study.

The maximum claudication distance was determined by walking the patient on a horizontal treadmill[7] at 3·5 km/h. Each patient exercised on five separate occasions (randomized), carrying weights of 0, 2·5, 5, 7·5 and 10 kg in a waist belt. Ankle and brachial arterial pressures were measured both before and after exercise to confirm the diagnosis of intermittent claudication. A minimum rest period of 30 min was allowed between each exercise test.

For each patient the reduction in claudication distance per kilogram load was calculated and referred to as the response index (RI):

$$RI=\frac{CD_0-CD_{10}}{10}\ \mathrm{m/kg}$$

where CD_0 and CD_{10} represent claudication distance with 0 and 10 kg weights, respectively.

Patients were further categorized as mild or severe claudicants according to whether they could walk a distance of 200 m. Results are expressed as mean(s.e.m.).

Results

Table 1 shows that the maximum claudication distance was significantly reduced when carrying 5 kg or more ($P<0{\cdot}01$, paired Wilcoxon test). A linear relationship was demonstrated between the mean claudication distance and the load carried ($r=0{\cdot}98$, $P<0{\cdot}01$, Pearson's test). All but one patient walked less far on the treadmill when carrying the full 10 kg (*Figure 1*). The mean decrease in claudication distance for all patients was 102 m for each 10 kg of weight carried; RI = 10·2(3·6) m/kg.

Six patients were graded as mild and 14 as severe claudicants (*Figure 2*). When carrying a 10 kg load, a mean decrease in claudication distance of 259 m was noted for the mild claudicants compared with 33 m for the severe claudicants. Statistical significance was obtained in both claudication groups when carrying 5 kg or more ($P<0{\cdot}05$, paired Wilcoxon test). The mean(s.e.m.) response index of the severe group, RI = 3·3(0·8), was significantly less than that of the mild group, RI = 25·9(9·5) ($P<0{\cdot}01$, Mann–Whitney U test).

Discussion

Intermittent claudication is a common and often debilitating complaint of varying severity. It affects 2 per cent of the population aged over 50 years[8,9], and in most cases is associated with cigarette smoking, hypertriglyceridaemia and diabetes[9–11]. The natural history of claudication is varied; 50 per cent of

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Table 1 *The effect of weight on claudication distance*

	Claudication distance (m) according to load (kg)					Response index (m/kg)
	0	2·5	5	7·5	10	
All	249(61)	231(58)	206(51)*	158(56)*	147(36)*	10·2(3·6)
Mild	567(132)	518(134)	448(122)†	380(82)†	308(90)†	25·9(9·5)†
Severe	112(12)	108(13)	102(14)†	85(12)†	79(11)†	3·3(0·8)†

Values are mean(s.e.m.). * $P<0·01$; † $P<0·05$

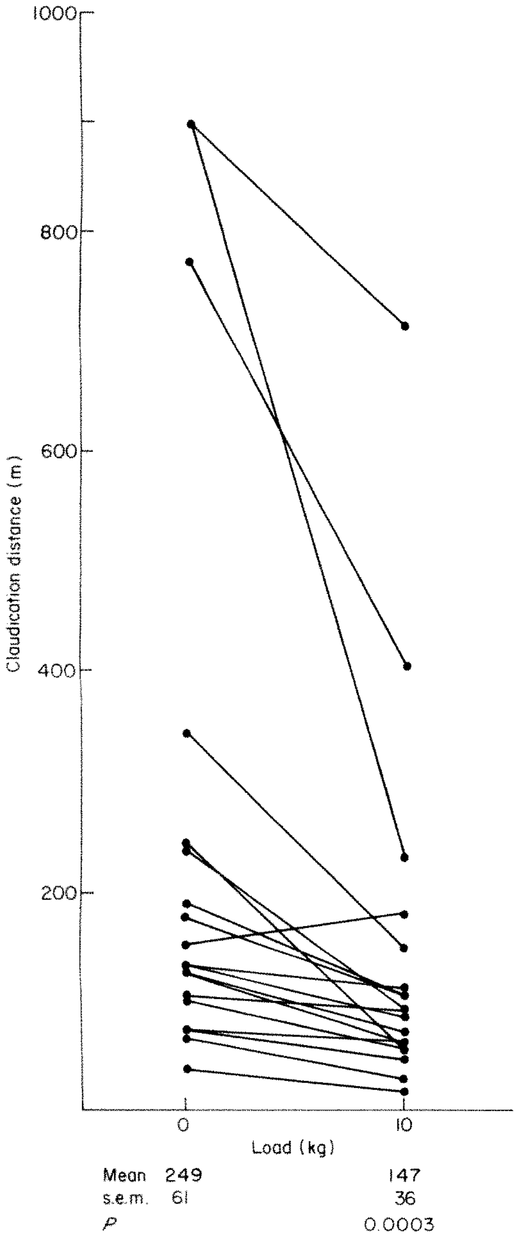

Figure 1 *The effect of weight on claudication distance. Response to 10 kg load for all patients* (n = *20; two patients walked the same distance at 0 kg and at 10 kg*). *0 kg, mean(s.e.m.) 249(61) m; 10 kg, mean(s.e.m.) 147(36) m;* P = *0·0003*

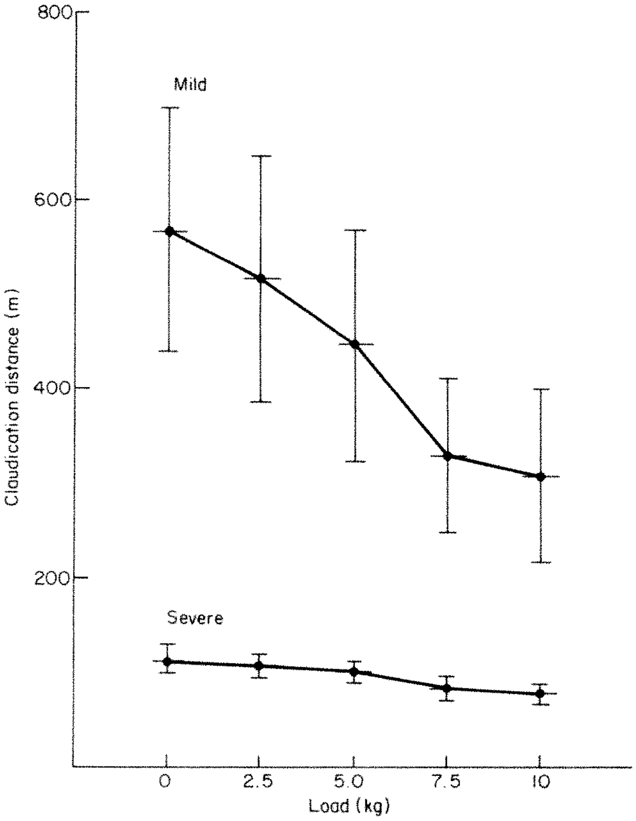

Figure 2 *The effect of weight on claudication distance. Results for severe* (n = *14*) *and mild* (n = *6*) *claudicant groups. Values plotted are mean(s.e.m.)*

patients remain stable or improve on cessation of smoking, 9 per cent a year require surgery and 4 per cent die[12–15].

Conservative management of claudication remains the mainstay of treatment, with interventional treatment (balloon angioplasty and surgery) reserved for those who are severely or progressively incapacitated[6].

One of the main fears of patients with a diagnosis of intermittent claudication is that of disease progression resulting in gangrene and amputation. Most patients with stable claudication may be reassured about amputation, particularly if they stop smoking[16]. In many patients walking distance is improved and cessation of smoking may be the only treatment required[17].

In motivated individuals the addition of an exercise programme can quicken the improvement in symptoms, reflected by an increase in their maximum tolerated walking distance. This is thought to be secondary to collateral vessel dilatation and blood viscosity reduction[18], but may also involve redistribution of muscle blood flow within the leg, increased metabolic activity in exercise-trained skeletal muscle[19,20], improved walking efficiency and increased pain tolerance[2]. A recent report has suggested that, in patients with mild or moderate claudication, supervised exercise therapy may ultimately produce greater symptomatic improvement than balloon angioplasty[16].

The role of weight loss in improvement in claudication distance is unclear[6]. Although obesity may be determined genetically[21], the lifestyle characteristics influencing obesity most, namely diet[22] and physical activity[23], are themselves related to morbidity and mortality, albeit indirectly[5]. Moreover, some patients who do succeed in stopping smoking may actually increase in weight with resultant worsening of their claudication distance. Because of these complex interrelations it is virtually impossible to isolate the true independent impact of weight on claudication. Nevertheless, this study has shown that an increase in the load carried by a patient can significantly reduce the maximum claudication distance. By performing all five treadmill tests during a single clinic visit, variables such as diet, smoking and exercise cannot influence the results. Furthermore, randomization of the order in which each test was performed has minimized factors such as patient fatigue and equipment familiarity, which may themselves have an influence on results.

In this patient group, for each kilogram of load added, the maximum walking distance was reduced by 10·2 m. The high response index noted in mild compared with severe claudicants suggests that the mild claudicants would benefit most from weight reduction.

For those claudicants who are not initially over-weight, cessation of smoking and commencement of a regular exercise programme are of prime importance. However, many patients with mild claudication are elderly and obese, often with associated hyperlipidaemic states and reduced cardiorespiratory reserve; for this group exercise training is less beneficial and may even be contraindicated[2]. We would recommend commencement of a low fat, weight-reducing diet for these patients. Weight loss would be beneficial, not only with respect to the mechanical improvement in walking distance associated with decreased lower limb loading, but also because it results in lower blood lipid concentrations and a possible reduction in both coronary and peripheral vasculature atherosclerosis progression[4,24–27].

In summary, obese, elderly patients with mild claudication should stop smoking and lose weight. With increasing weight reduction, exercise programmes will become both safer and easier, and maximal claudication distances will improve.

References

1. Housley E. Treating claudication in 5 words. *Br Med J* 1988; **296**: 1483–4.
2. Clifford PC, Davies PW, Hayne JA, Baird RN. Intermittent claudication. Is a supervised exercise class worthwhile? *Br Med J* 1980; **280**: 1503–5.
3. Jonason T, Bergström R. Cessation of smoking in patients with intermittent claudication. *Acta Med Scand* 1987; **221**: 253–60.
4. Hubert HB, Feinleib M, McNamara PM *et al.* Obesity is an independent risk factor for cardiovascular disease: a 26 year follow-up of participants in the Framlington Study. *Circulation* 1983; **67**: 968–77.
5. Tuomilehto J, Salonen JT, Marti B *et al.* Body weight and risk of myocardial infarction and death in the adult population of eastern Finland. *Br Med J* 1987; **295**: 623–7.
6. Anon. Management of intermittent claudication. *Lancet* 1980; **i**: 404–5.
7. Laing SP, Greenhalgh RM. Standard exercise test to assess peripheral arterial disease. *Br Med J* 1980; **i**: 13–16.
8. Hughson WG, Mann JI, Garrod A. Intermittent claudication: prevalence and risk factors. *Br Med J* 1978; **i**: 1379–81.
9. Reunanen A, Tukkunen H, Aromaa A. Prevalence of intermittent claudication and its effect on mortality. *Acta Med Scand* 1982; **211**: 249–56.
10. Fowkes FG. Epidemiology of atherosclerotic arterial disease in the lower limbs. *Eur J Vasc Surg* 1988; **2**: 283–91.
11. Greenhalgh RM, Rosengarten DS, Mervart I *et al.* Serum lipids and lipoproteins in peripheral vascular disease. *Lancet* 1971; **ii**: 947–50.
12. Mathieson FR, Larsen EE, Wulff MR. Some factors influencing the spontaneous course of arterial vascular insufficiency. *Acta Chir Scand* 1970; **136**: 303–8.
13. Jelnes R, Gaardsting O, Jensen KH *et al.* Fate of intermittent claudication: outcome and risk factors. *Br Med J* 1986; **293**: 1137–40.
14. Cronenwett JL, Warner KG, Zelenock GB *et al.* Intermittent claudication. Current results of non-operative management. *Arch Surg* 1984; **119**: 430–6.
15. Imparato AM, Kim G, Davidson T, Crowley JG. Intermittent claudication: its natural course. *Surgery* 1975; **78**: 795–9.
16. Creasy TS, McMillan PJ, Fletcher EWL, Collin J, Morris PJ. Is percutaneous angioplasty better than exercise for claudication? Preliminary results from a prospective randomised trial. *Eur J Vasc Surg* 1990; **4**: 135–40.
17. Foley WT. Treatment of gangrene of the feet and legs by walking. *Circulation* 1957; **15**: 689–700.
18. Skinner JS, Strandness DE. Exercise and intermittent claudication II; effect of physical training. *Circulation* 1967; **36**: 23–9.
19. Dahllöf AG, Holm J, Schersten T, Sivertsenn R. Peripheral arterial insufficiency; effect of physical training on walking tolerance, calf blood flow and blood flow resistance. *Scand J Rehab Med* 1976; **8**: 19–26.
20. Gollnick PD, Armstrong RB, Saubert CW *et al.* Enzyme activity and fibre composition in skeletal muscle of untrained and trained men. *J Appl Physiol* 1972; **33**: 312–19.
21. Stunkard AJ, Sörensen TI, Hanis C *et al.* An adoption study of human obesity. *N Engl J Med* 1986; **314**: 193–8.
22. Kromhout D, de Lezenne C, Coulander C. Diet, prevalence and 10-year mortality from coronary heart disease in 871 middle aged men. *Am J Epidemiol* 1984; **119**: 733–41.
23. Paffenbarger RS, Hyde RT, Wing AL, Hseih CC. Physical activity, all-cause mortality and longevity of college alumni. *N Engl J Med* 1986; **314**: 605–13.
24. Jarrett RJ, Shipley MJ, Rose G. Weight and mortality in the Whitehall study. *Br Med J* 1982; **285**: 535–7.
25. Keys A, Menotti A, Aravanis C *et al.* The seven countries study: 2289 deaths in 15 years. *Prev Med* 1984; **13**: 141–54.
26. Hubert HB. The importance of obesity in the development of coronary risk factors and disease. *Annu Rev Public Health* 1986; **7**: 493–502.
27. Barrett-Connor E. Obesity, atherosclerosis, and coronary artery disease. *Ann Intern Med* 1984; **103**: 1010–19.

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Role of splenectomy as a salvage procedure in thrombotic thrombocytopenic purpura

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Thrombotic thrombocytopenic purpura is a rare but serious haematological disease for which first-line therapy is medical, but not always successful. The role of splenectomy in the management of such patients is unclear. This paper reports three patients with the condition who went into remission following splenectomy after other forms of therapy had failed. Because thrombotic thrombocytopenic purpura is nearly always fatal if a remission is not obtained, splenectomy should be considered in patients who prove to be resistant to medical therapy.

Thrombotic thrombocytopenic purpura, first described by Moschcowitz in 1924[1], is a rare syndrome characterized by thrombocytopenia, microangiopathic haemolytic anaemia, fever, neurological symptoms and renal involvement. Any of the last three features may be absent at the time of presentation. The aetiology of the condition is not clearly defined. Numerous forms of therapy have been reported to have varying degrees of efficacy and include corticosteroids, heparin, antiplatelet drugs, immunosuppressive agents, immunoglobulins, splenectomy, prostacyclin infusion, whole blood exchange transfusion, plasma transfusion and plasma exchange with fresh frozen plasma[2]. Plasma transfusion and plasma exchange appear to be the most successful forms of treatment, with approximately 70–80 per cent of patients responding to some form of manipulation with fresh plasma[3,4]. Twenty to thirty per cent of patients fail to respond or relapse after initial response and there is no consensus as to the best form of treatment for these cases. If a remission is not obtained then the condition is nearly always fatal. The effects of splenectomy, as a salvage manoeuvre, in three such patients in whom all other therapy had failed are reported.

Patients

Case 1

A 24-year-old West Indian man was admitted in coma. The blood count was haemoglobin 7·5 g/dl, white blood cells 19·4 × 10^9/l, platelets 22 × 10^9/l, with a blood film showing microangiopathic changes. Thrombotic thrombocytopenic purpura was diagnosed and the patient was treated with daily fresh plasma exchange (2·2 litres), prednisolone, aspirin and dipyridamole. His clinical condition improved rapidly and the platelet count returned to normal by 12 days. Treatment was gradually withdrawn over 6 months.

The patient had two relapses, 5 and 6 years after the initial attack, responding rapidly to plasma exchange, prednisolone, aspirin and dipyridamole. At a third relapse 8 years after the initial episode he failed to respond and, because of deteriorating renal function, splenectomy was carried out after platelet and red cell transfusions. Plasma exchange was continued with aspirin and dipyridamole. The platelet count started rising on the day after splenectomy and reached a normal level after 6 days. The blood count and serum creatinine level became normal 4 weeks after splenectomy. The patient remains well 30 months after splenectomy.

Case 2

A 33-year-old West Indian woman gave birth to a full-term baby by elective caesarian section after a normal pregnancy. She had a history of two previous uneventful pregnancies. On the ninth day after delivery a blood count showed a haemoglobin concentration of 12·7 g/dl, white blood cells 6·3 × 10^9/l, platelets 30 × 10^9/l, with microangiopathic changes on the blood film. Thrombotic thrombocytopenic purpura was diagnosed but no treatment was started. Three days later purpura developed and a blood count showed a platelet concentration of 6 × 10^9/l. Plasma transfusions were started at a dose of 1·0 l/day with 60 mg prednisolone daily. The patient remained asymptomatic, but her platelet count showed only a minimal response over the next 10 days, and she required red cell transfusions. Fresh plasma exchange at a rate of 3·0 l/day, 75 mg aspirin daily, 100 mg dipyridamole three times daily and prostacyclin (epoprostenol) infusion were ineffective. The patient underwent splenectomy 26 days after the diagnosis of thrombotic thrombocytopenic purpura. Her platelet count reached a normal level 12 days after splenectomy. Other treatments were slowly withdrawn and she remains well with a normal blood count 3 years after splenectomy.

Case 3

A 33-year-old pregnant Japanese woman was admitted with purpuric spots on her legs which had been present for 5 days. Her blood count was haemoglobin 8·6 g/dl, white blood cells 4·8 × 10^9/l and platelets 7 × 10^9/l, with microangiopathic changes on the blood film. Thrombotic thrombocytopenic purpura was diagnosed. She initially responded to fresh plasma exchange at a rate of 2·9 l/day with 60 mg prednisolone daily but on withdrawal experienced an immediate relapse. In view of her failure to respond, the pregnancy was terminated (under platelet cover) 14 days after diagnosis of the condition. There was no response over the next 7 days and splenectomy was performed 3 weeks after initial diagnosis. Her platelet count returned to normal 4 days after splenectomy. Fresh plasma transfusions and prednisolone were gradually withdrawn and her blood count and morphology gradually returned to normal. She remains asymptomatic with a normal blood count 6 months after splenectomy.

Discussion

The cause of thrombotic thrombocytopenic purpura is unknown but it may rarely occur in association with pregnancy and the postpartum period[5,6], various drugs[2], connective tissue disorders[7,8], neoplastic disorders[2] or bacterial endocarditis[9]. The majority of cases are idiopathic[10]. The characteristic pathological finding is of widespread multiorgan hyaline thrombi, containing varying amounts of platelets and fibrin, and associated with endothelial proliferation. Numerous organs are involved, most commonly the kidneys, brain, heart, adrenals and pancreas[11]. At times the thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome are difficult to separate and the pathogenesis of both conditions may be similar. Coagulation studies and fibrinogen levels are normal in thrombotic thrombocytopenic purpura, excluding it as a form of disseminated intravascular coagulation.

Treatment is largely empirical. More recently, however, whole blood exchange transfusion[12,13], plasma transfusion[14,15] and plasma exchange with fresh frozen plasma[16] have resulted in much better responses. Plasma exchange with fresh frozen plasma is now the treatment of choice, presumably either supplying missing factors or removing harmful ones or both.

Approximately 70–80 per cent of patients respond to some form of plasma manipulation[3,4]. There is no consensus as to the best way of treating patients who fail to respond or who

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relapse after an initial beneficial response[17]. Splenectomy alone, used as a first-line therapeutic option, does not appear to be effective[15,18,19]. Some reports have suggested that splenectomy might have a role to play as a salvage procedure in those patients who are unresponsive to all other forms of therapy[20-22]. All three patients described here showed an immediate, dramatic and sustained response to splenectomy, after all other treatment options had been tried. The mechanism whereby splenectomy exerts its beneficial effect in these cases is unknown. Splenectomy should be considered whenever patients with thrombotic thrombocytopenic purpura prove resistant to other forms of treatment.

References

1. Moschcowitz E. Hyaline thrombosis of the terminal arteries and capillaries: a hitherto undescribed disease. *Proc New York Pathol Soc* 1924; **24**: 21-4.
2. Ruggenenti P, Remuzzi G. Thrombotic thrombocytopenic purpura and related disorders. *Hematol Oncol Clin North Am* 1990; **4**: 219-41.
3. George JN, Aster RH. Thrombocytopenia due to enhanced platelet destruction by nonimmunological mechanisms. In: Williams WJ, Beutler E, Ersley AJ, Lichtman MA, eds. *Haematology*. New York: McGraw Hill, 1990: 1351-69.
4. Liu ET, Linker CA, Shuman MA. Management of treatment failure in thrombotic thrombocytopenic purpura. *Am J Hematol* 1986; **23**: 347-61.
5. Ridolfi RL, Bill WR. Thrombotic thrombocytopenic purpura. *Medicine* 1981; **60**: 413-28.
6. Schwartz ML, Brenner WE. The obfuscation of eclampsia by thrombotic thrombocytopenic purpura. *Am J Obstet Gynecol* 1978; **131**: 18-24.
7. Naeme PB. Immunologic and other factors in thrombotic thrombocytopenic purpura (TTP). *Semin Thromb Hemost* 1980; **6**: 416-22.
8. Dekker A, O'Brien ME, Cammarata RJ. The association of thrombotic thrombocytopenic purpura with systemic lupus erythematosus. *Am J Med Sci* 1974; **267**: 243-9.
9. Moore MR, Poon MC. Syndrome resembling thrombotic thrombocytopenic purpura associated with bacterial endocarditis. *South Med J* 1980; **73**: 541.
10. Machin SJ. Clinical annotation: thrombotic thrombocytopenic purpura. *Br J Haematol* 1984; **56**: 191-7.
11. Berkowitz LR, Daldorf FG, Blatt PM. Thrombotic thrombocytopenic purpura. A pathology review. *JAMA* 1979; **241**(2): 1709-10.
12. Bukowski RM, Hewlett JS, Harris JW *et al.* Exchange transfusions in the treatment of thrombotic thrombocytopenic purpura. *Semin Hematol* 1976; **13**: 219-27.
13. Pisciotta AV, Garthwaite T, Darin J, Aster RH. Treatment of thrombotic thrombocytopenic purpura by exchange transfusion. *Am J Hematol* 1977; **3**: 73-8.
14. Byrnes JJ, Khurana M. Treatment of thrombotic thrombocytopenic purpura with plasma. *N Engl J Med* 1977; **297**: 1386-9.
15. Petitt RM. Thrombotic thrombocytopenic purpura: a thirty year review. *Semin Thromb Hemost* 1980; **6**: 350-5.
16. Bukowski RM. Thrombotic thrombocytopenic purpura: a review. In: Spaet TH, ed. *Progress in Hemostasis and Thrombosis*. New York: Grune and Stratton, 1982: 287-337.
17. Bukowski RM, Hewlett JS, Reimer RR. Therapy of thrombotic thrombocytopenic purpura: an overview. *Semin Thromb Hemost* 1981; **7**: 1-8.
18. Amorosi EL, Ultmann JE. Thrombotic thrombocytopenic purpura. Report of 16 cases and review of the literature. *Medicine* 1966; **45**: 139-59.
19. Kennedy SS, Zacharski LR, Beck JR. Thrombotic thrombocytopenic purpura: analysis of 48 unselected cases. *Semin Thromb Hemost* 1980; **6**: 341-50.
20. Cuttner J. Thrombotic thrombocytopenic purpura: a ten year experience. *Blood* 1980; **56**: 302-6.
21. Schneider PA, Rayner AA, Linker CA, Schuman MA, Liu ET, Hohn DC. The role of splenectomy in multimodality treatment of thrombotic thrombocytopenic purpura. *Ann Surg* 1985; **202**: 318-22.
22. Thompson HW, McCarthy LJ. Thrombotic thrombocytopenic purpura. Potential benefit of splenectomy after plasma exchange. *Arch Intern Med* 1983; **143**: 2117-19.

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Peripheral parenteral nutrition: effect of a standardized compounded mixture on infusion phlebitis

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The incidence and severity of infusion phlebitis was evaluated prospectively in 142 surgical patients who received peripheral parenteral nutrition (PPN) for a total of 700 days. In a first study phase 83 patients were given PPN for a total of 424 days. All nutrient solutions were delivered over a 12-h period from a 3-litre bag and the infusion sites rotated daily. These methods resulted in an incidence of phlebitis of 18 per cent, 75 per cent of the patients being fed successfully by PPN until resumption of oral nutrition. In an attempt to assess the importance of the method of delivering nutrient solutions, the next 59 patients were randomized to receive PPN as a compounded mixture or by a conventional technique with simultaneous infusion from separate bottles. Infusion phlebitis was significantly more frequent ($P<0.001$) *in patients infused with separate bottles. There was no difference between the groups with regard to duration of nutrition or the need to establish central venous access. We conclude that PPN is a safe and cost-effective means of providing total parenteral nutrition in most surgical patients. The use of compounded mixtures significantly reduces the incidence of phlebitis without increasing total costs.*

The most common complications associated with total parenteral nutrition (TPN) are related to the use of central venous catheters. Administration of TPN solutions by peripheral veins avoids these complications and there have been several reports on its successful application[1-3]. However, many authorities feel that the incidence of phlebitis precludes effective nutritional support in all but a few patients. Further, the practical problems encountered when bottles of nutrient solutions with widely differing specific gravities are infused have prohibited widespread adoption of peripheral parenteral nutrition (PPN) as routine practice.

Several recent developments have occurred which may render these objections invalid. First, it has been shown that the incidence of infusion phlebitis may be significantly reduced by frequent changes of peripheral access sites[4]. Second, it is now well established that the protein and energy requirements of most surgical patients are such that the total volume of nutrient fluids required rarely exceeds 3 litres[5,6]. Finally, it is now generally accepted that compounded mixtures of nutrient solutions are safe and the possibility of administering them from a single 3-litre bag may in itself reduce the incidence of phlebitis through avoidance of the practical difficulties encountered with multiple bottle infusions, particularly when solutions with differing specific gravities are used. The aim of this study was to evaluate the efficacy of PPN with particular regard to the effects of frequent changes in peripheral venous access sites, together with an assessment of the practical benefit of using compounded mixtures and the influence of this on the incidence of infusion phlebitis.

Patients and methods

Patients

A total of 142 consecutive patients entered this study in which the first 83 (group I) all received PPN as a compounded mixture from a 3-litre bag. The following 59 patients (group II) were randomized to receive PPN either as a compounded mixture (PPN-A) or from conventional bottles infused simultaneously (PPN-B). The patients' diagnoses included gastrointestinal malignancies ($n=69$), inflammatory bowel disease ($n=18$), various other gastrointestinal inflammatory states (diverticulitis, pancreatitis, cholecystitis; $n=20$), gastric or duodenal ulcers ($n=9$) and ileus, abdominal infections, fistulae and various other disease states ($n=26$). Patients with hepatic, renal or cardiac failure or those with inadequate veins were not entered into the study. The characteristics of the patients are presented in *Table 1*.

Study protocol

Patients who were predicted not to be able to satisfy their nutrient requirements by mouth within 4 days were entered into the study. An identical technique for peripheral vein TPN based on the recommendations of Hessov *et al.*[4] was used in all four surgical departments. The instructions were to use the largest possible arm vein, to avoid the veins of the back of the hands, to use thin (1·0 mm diameter) short plastic cannulae, to complete the daily nutritional programme

Table 1 *Clinical details of patients*

		Group II	
	Group I	PPN-A	PPN-B
Number of patients	83	30	29
Sex ratio (M:F)	52:31	15:15	16:13
Mean(s.d.) age (years)	59(17)	61(14)	67(12)
Mean(s.d.) weight (kg)	68(13)	67(15)	72(16)
Calculated mean(s.d.) basal metabolic rate (kcal/day)	1453(242)	1398(261)	1462(292)
Weight loss*			
None	42 (51)	19 (63)	21 (72)
< 10%	27 (33)	8 (27)	4 (14)
> 10%	14 (17)	3 (10)	4 (14)
	83 (100)	30 (100)	29 (100)
Ratio of cancer:no cancer	42:41	20:10	21:8
Ratio of operation:no operation	63:20	22:8	24:5

*Values in parentheses are percentages

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within 12 h, to remove the catheter immediately after completing the infusion, and to change the infusion site to the contralateral arm the following day. The infusion site was documented on a protocol sheet and was examined daily during the first 3 days after termination of the infusion to record the appearance of delayed vein complications.

Phlebitis was graded according to a modified Maddox classification[7]: grade 0, no pain, erythema, swelling, induration or palpable venous cord; grade 1, painful intravenous site; grade 2, painful intravenous site with erythema, swelling or both; grade 3, painful intravenous site, erythema, swelling and induration or palpable venous cord.

Routine blood chemistry was recorded in all patients on entry into the study and every 3 days thereafter. The basal metabolic rate was calculated from standard tables based on sex, age, height and weight[8].

Intravenous nutrients

A 3-litre ethylene vinyl acetate bag (The IV Bag, Kabi Pharmacia AB, Stockholm, Sweden) was used as a container for the compounded mixture. The fat source was Intralipid 20 per cent (Kabi Pharmacia AB) when compounded mixtures were used and Intralipid 10 per cent when parenteral nutrition was provided by simultaneous infusion of separate bottles. Crystalline amino acids were given in the form of Vamin 9 g/l-Glucose (Kabi Pharmacia AB), which contains 10 per cent glucose. Glucose 10 per cent with electrolytes (Na^+ 40 mmol, K^+ 20 mmol) and Glucose 5 per cent (Kabi Pharmacia AB) were used as additional glucose sources. Trace elements (Addamel, Kabi Pharmacia AB), phosphate (Addiphos, Kabi Pharmacia AB), water and fat soluble vitamins (Soluvit Novum and Vitalipid Novum, Kabi Pharmacia AB) were added according to the manufacturer's instructions. The two TPN systems contained identical amounts of energy (2050 kcal, 8·6 kJ) and nutrients: 9 g nitrogen, 100 g fat, 225 g glucose, 97·5 mmol Na^+, 47·5 mmol K^+, 17·5 mmol phosphate, 7·5 mmol Ca^{2+}, 4·5 mmol Mg^{2+} and 100 mmol Cl^-. The volume of the compounded mixture was 3025 ml, osmolarity 820 mOsm/kg water and pH was 5·4. The compounded mixtures were prepared at the local hospital pharmacies.

Analysis of cost-effectiveness

A cost-effectiveness analysis of the two approaches to PPN was performed. The costs of all preparations, solutions and materials used in association with PPN were listed and the time taken by nurses and pharmacists was translated into labour costs to obtain a mean daily cost per patient.

Statistical analysis

The duration of TPN was analysed by the Kaplan–Meier survival curve technique. Additional statistical analyses included the Wilcoxon rank sum test and the χ^2 test. All data are presented as mean(s.d.).

Results

There were no significant differences in sex, age, weight or calculated basal metabolic rate between the groups (*Table 1*). The degree of prior weight loss and the proportion of patients with cancer or previous operation did not differ significantly between the groups. Seventy-five per cent of the patients had undergone an abdominal operation; mean(s.d.) time from operation to the initiation of TPN in these patients was 2·6(1·3) days.

Group I patients were given PPN for a mean(s.d.) period of 5·4(3·3) days. In this group, three-quarters of the patients could be fed by peripheral veins until resumption of oral nutrition (*Table 2*). Twelve patients (14·5 per cent) had to have central venous catheters inserted following failure of PPN; another 8(9·6 per cent) were switched to central venous TPN for reasons which were not attributable to phlebitis of peripheral veins or to any other technical problems associated with PPN. Most of these patients required surgery or haemodynamic monitoring and central venous catheters were inserted to facilitate general treatment.

In group II, the mean(s.d.) duration of intravenous feeding was not significantly different in PPN-A and PPN-B (4·6(2·5) *versus* 3·9(1·4) days; $P>0·05$; *Table 2*). Most of the patients in both groups could be fed through peripheral veins until oral resumption was possible. The proportion of patients that had to be changed from PPN to central venous catheter infusions tended to be higher in PPN-B than in PPN-A, but the difference was not statistically significant.

The incidence and severity of phlebitis is shown in *Table 3*. On daily inspection, there was no evidence of phlebitis in 81·9 per cent of patients in group I. In group II, peripheral vein tolerance was found to be markedly better in patients randomized to receive the compounded mixture (PPN-A) than in those fed from separate bottles (PPN-B). The daily incidence of grade 1 as well as grade 2 phlebitis was 3–5 times higher in the PPN-B than in the PPN-A group ($P<0·001$).

The percentage of patients remaining on PPN is shown in *Figure 1*. Although most patients had finished with PPN within 5–6 days, a few were fed for several weeks by peripheral vein.

There was no significant change in body weight during the course of PPN (*Table 2*). Blood chemistry analyses showed no significant changes after completion of PPN compared with pre-PPN values (data not shown). The total costs were

Table 2 *Outcome of peripheral parenteral nutrition (PPN)*

		Group II	
	Group I (n = 83)	PPN-A (n = 30)	PPN-B (n = 29)
Number of PPN days	447	139	114
Mean(s.d.) duration of PPN (days)	5·4(3·3)	4·6(2·5)	3·9(1·4)
Outcome*			
PPN until oral resumption	63 (76)	23 (77)	20 (69)
Change to central catheter	12 (14)	4 (13)	6 (21)
PPN not completed for other reasons	8 (10)	3 (10)	3 (10)
Weight change (%) during PPN	+0·6	+0·1	+0·3

*Values in parentheses are percentages

Table 3 *Incidence and severity of phlebitis*

Phlebitis		Group II	
Maddox grade	Group I	PPN-A	PPN-B
0	366 (81·9)	116 (83·5)	46 (40·4)*
1	35 (7·8)	11 (7·9)	30 (26·3)*
2	37 (8·2)	10 (7·2)	37 (32·5)*
3	9 (2·1)	2 (1·4)	1 (0·9)
Total	447	139	114

Values in parentheses are percentages. *$P<0·001$ (PPN-A *versus* PPN-B)

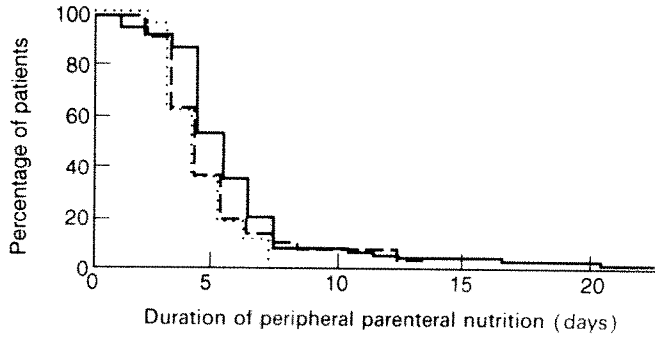

Figure 1 *Duration of peripheral parenteral nutrition. Patients included in group I (——) received compounded mixtures but were not randomized (n = 83). Patients in group II were randomized either to receive a compounded nutrient mixture (PPN-A, n = 30, – – –) or were infused from separate bottles (PPN-B, n = 29, · · · · · ·). Numbers receiving PPN at day 5: group I, 44; PPN-A, 11; PPN-B, 10; at day 10: group I, 7; PPN-A, 3*

Table 4 *Mean daily cost per patient (in Swedish crowns)* of peripheral parenteral nutrition given as a compounded mixture (PPN-A) or from separate bottles (PPN-B). Four patients in each group were evaluated*

	PPN-A	PPN-B
Solutions	663	663
Equipment for preparation/administration	107	50
Pharmacist	61	–
Nursing	24	86
Total	855	799

*£1 sterling = 10·7 Swedish crowns

7 per cent higher for PPN-A than for PPN-B (*Table 4*). This difference was entirely accounted for by higher costs for materials. The labour costs for the two systems were found to be identical.

Discussion

This study shows that it is possible to supply a large percentage of surgical patients with TPN without the use of central venous catheters. Compared with the traditional way of providing TPN from separate infusion bottles, the use of a compounded mixture was associated with a significantly lower incidence of phlebitis. The local complication rate observed was in fact similar to the incidence of phlebitis found by others in patients receiving isotonic glucose solutions or various other non-nutritional infusates[7,9–11].

There have been several reports on the successful use of peripheral vein TPN using glucose, fat and amino acids[1–3], but the incidence of local vein complications has not usually been reported. In studies where peripheral vein complication rates have been documented, they have been in the range of 15–50 per cent[12,13]. This wide range seems mainly to be related to differences in the osmolarity and pH of the infused nutrients, the techniques used for their administration, and to definitions of vein complications.

Hypertonicity and a non-physiological pH are factors which have been shown to have a negative influence on vein tolerance. The osmolarity of the compounded mixture (820 mOsm/kg water) is within the range associated with an acceptably low incidence of phlebitis[14], but the pH of the mixture may be lower than optimal[15].

There are two ways of delivering solutions by peripheral vein: either the infusion site is changed before severe phlebitis has occurred or the same vein is used as long as is practically feasible. The incidence of phlebitis during the infusion of hypocaloric solutions has been shown to be almost zero with infusion periods shorter than 12 h[15,16] but may approach 100 per cent if infusions are continued for 4–5 days[17]. Clinical as well as experimental[18] studies show that the risk of phlebitis increases with the length of the infusion time. In a study by Elliot *et al.*[18], the phlebitis rate was 5 per cent during the first 24 h of infusion of a compounded mixture, but since the same insertion site was used as long as feasible, the cumulative rate of phlebitis was 27 per cent. In other studies where peripheral vein nutrition has been given in amounts intended to cover energy requirements, the daily incidence of phlebitis has not been reported but the cumulative rate of phlebitis has been 47–77 per cent[12,19]. In the present study the incidence of phlebitis per infusion day for patients receiving compounded mixtures was 18 per cent. The practice of rotating the cannulation site was probably an important factor in the comparatively low frequency of phlebitis. Another reason for rotating the cannulation site is that it is usually not possible to predict beforehand which patient will require TPN for more than 3–5 days which is the maximum time that a particular intravenous site can be used. Two patients in the present study tolerated peripheral vein TPN for 3 weeks and it is improbable that this could have been achieved if the technique of rotating sites had not been used.

It has been pointed out that signs of phlebitis may develop several days after an infusion[20]. In the present study the peripheral vein status did not change during the following 2 days in 80 per cent of the insertion sites used. In 10 per cent of the cases a deterioration of vein status was noted after completion of the infusion but improvement was observed in a similar proportion. The appearance of delayed phlebitis was not considered a problem in the present study and did not hinder later use of a previously used insertion site.

The standard diets were designed to cover nutritional requirements. The daily energy intake was 2050 kcal (8·6 kJ), including protein calories and the mean estimated basal metabolic rate was below 1500 kcal/day (6·3 kJ/day) in all three groups. MacFie conducted an energy balance study in patients before and after surgery and found the energy expenditure for physical activity to be of the order of 500 and 250 kcal/day (2·1 and 1·05 kJ/day) respectively[21]. There was no significant weight change in our patients, and the measured albumin and sodium plasma concentrations did not indicate any significant water retention. It thus seems that the energy supply was sufficiently high to cover energy requirements. Blood chemistry showed that plasma concentrations of potassium, chloride and phosphate were maintained during the course of TPN. The solutions obviously contained sufficient amounts of these electrolytes. For all practical purposes, the standardized regimens provided adequate nutrition.

The mechanism behind the better vein tolerance observed when using compounded mixtures is not known. During infusions from separate bottles, a period of higher osmolarity (fat plus amino acid/glucose) is followed by a period of lower osmolarity (fat plus glucose). It is possible that the administration of nutrients with higher osmolarity may have contributed to the higher incidence of phlebitis observed with the separate bottle infusion system compared with that seen with the stable osmolarity provided by the compounded mixture.

The randomization of patients in group II made it possible to perform a cost-effectiveness analysis of the two approaches to PPN. The labour costs for PPN-A and PPN-B were identical (*Table 4*). However, the use of compounded mixtures as opposed to separate bottles was associated with a reduction by two-thirds of nursing costs but increased the costs of pharmacy to a similar extent. Thus, the use of compounded mixtures is associated with a shift from nursing to pharmacist costs. The higher total cost (7 per cent) for PPN-A was entirely accounted for by higher costs for materials; however, the inclusion of costs related to the higher percentage of changes from peripheral to central venous catheters in the PPN-B group (20·7 per cent), compared with the PPN-A group (13·3 per cent), virtually abolished the differences in costs between the two groups.

We conclude that the use of a compounded mixture and the technique of rotating infusion sites daily is associated with better peripheral vein tolerance compared with the infusion of nutrients from separate bottles. The use of a standardized compounded nutrient mixture during PPN is cost-effective because it reduces the incidence of phlebitis without increasing the total cost.

References

1. Dietel M, Kaminsky V. Total nutrition by peripheral vein – the lipid system. *Can Med Assoc J* 1974; **111**: 152–4.
2. Jeejeebhoy KN, Anderson GH, Nakhooda AF, Greenberg GR, Sanderson I, Marliss EB. Metabolic studies in total parenteral nutrition with lipid in man. Comparison with glucose. *J Clin Invest* 1976; **57**: 125–36.
3. Silberman H, Freehauf M, Fong G, Rosenblatt N. Parenteral nutrition with lipids. *JAMA* 1977; **238**: 1381–2.
4. Hessov I, Allen J, Arendt K, Gravholt L. Infusion thrombophlebitis in a surgical department. *Acta Chir Scand* 1977; **143**: 151–4.
5. Feurer ID, Crosby LO, Mullen JL. Measured and predicted resting energy expenditure in clinically stable patients. *Clin Nutr* 1984; **3**: 27–34.

6. Hansell DT, Richardson R, Davies JWL, Burns HJG. Estimation of resting energy expenditure by anthropometry. *Clin Nutr* 1987; **6**: 51–7.
7. Maddox RR, Rush DR, Rapp RP, Foster TS, Mazella V, McKean HE. Double-blind study to investigate methods to prevent cephalothin-induced phlebitis. *Am J Hosp Pharm* 1977; **34**: 29–34.
8. Harris JA, Benedict FG. Biometric studies of basal metabolism in man. Washington DC: Carnegie Institute of Washington 1919. Publication No. 279.
9. Fonkalsrud EW, Carpenter K, Masuda JY, Beckerman JH. Prophylaxis against postinfusion phlebitis. *Surg Gynecol Obstet* 1971; **133**: 253–6.
10. Falchuk KH, Peterson L, McNeil BJ. Microparticulate-induced phlebitis. Its prevention by in-line filtration. *N Engl J Med* 1985; **312**: 78–82.
11. Buxton AE, Highsmith AK, Garner JS *et al.* Contamination of intravenous infusion fluid: effects of changing administration sets. *Ann Intern Med* 1979; **90**: 764–8.
12. Daly JM, Masser E, Hansen L, Canham JE. Peripheral vein infusion of dextrose/amino solutions ±20% fat emulsion. *J Parent Enteral Nutr* 1985; **9**: 296–9.
13. Messing B, Leverve X, Rigand D *et al.* Peripheral venous complications of a hyperosmolar (960 mOsm) nutritive mixture: the effect of heparin and hydrocortisone. A multicenter double-blinded random study in 98 patients. *Clin Nutr* 1986; **5**: 57–61.
14. Bodoky A, Zbinden A, Müller J, Leutenegger A. Peripher-venöse Verträglichkeit hyperosmolarer Infusionslösungen. *Helv Chir Acta* 1980; **47**: 151–6.
15. Hessov I. Prevention of infusion thrombophlebitis. *Acta Anaesthesiol Scand* 1985; **29**: 33–7.
16. Collin J, Constable FL, Collin C, Johnston IDA. Infusion thrombophlebitis and infection with various cannulas. *Lancet* 1975; **i**: 150–3.
17. Comberg HU, Senninger N, Wagner M. Zur Frage der peripheren Venenverträglishkeit einer hyperosmolaren Basislösung. *Infusionstherapie* 1984; **11**: 262–5.
18. Elliot MJ, Heaviside DW, Broom J, Miller JDB. Cannulation site survival during peripheral intravenous feeding. *Br J Parent Ther* 1984; September: 202–7.
19. Kehoe JE, Mihranaian MH, Masser EL, Alcock N, Daly JM. Use of 20% fat emulsion in peripheral parenteral nutrition. *J Parent Enteral Nutr* 1984; **8**: 647–51.
20. Hästbacka J, Tammisto T, Elfing G, Tiitinen P. Infusion thrombophlebitis. *Acta Anaesthesiol Scand* 1966; **10**: 9–30.
21. MacFie J. Active metabolic expenditure of gastroenterological surgical patients receiving intravenous nutrition. *J Parent Enteral Nutr* 1984; **8**: 371–6.

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Case report

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Histological detection of microadenomas in the diagnosis of familial adenomatous polyposis

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Familial adenomatous polyposis (FAP) is an autosomal dominant genetic disorder in which colorectal adenomas develop in 15–20-year-olds with the almost inevitable progression of one or more to carcinoma 10–20 years later. Traditionally, screening of affected families has been by rigid sigmoidoscopy[1] but more recently detection of areas of congenital hypertrophy of the retinal pigment epithelium and analysis of blood samples for linked polymorphic DNA markers have been used in conjunction with large bowel endoscopy[2–4]. The diagnosis of FAP is established clinicopathologically when more than 100 adenomatous polyps are present in the large intestine. Rectal sparing has been reported[5,6], but is doubted by some[1,7]. Two *de novo* presentations of FAP are reported in which there were no rectal polyps but where microadenomas were detected histologically in the mucosa of the sigmoid colon. The implications of this finding are discussed.

Case reports

Patient 1

A 41-year-old woman underwent an emergency sigmoid colectomy (Hartmann's operation) for a perforated carcinoma of the sigmoid colon. There was no other palpable abnormality of the colon at that time. Macroscopically the resected specimen showed a perforated colonic cancer and no other abnormality, although microadenomas were detected on routine histological examination of the resection margins (*Figure 1*).

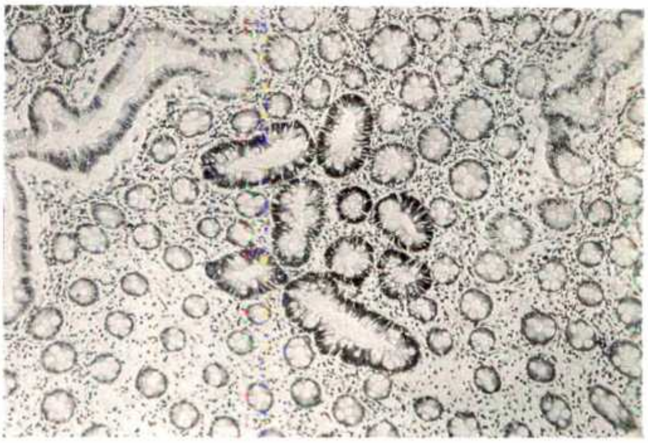

Figure 1 *An oligocryptal microadenoma from patient 1. This photomicrograph demonstrates adenomatous change in nine crypts which contrast with the adjacent normal crypts. Transverse sections of the mucosa such as this are useful to demonstrate small foci of adenomatous change (haematoxylin and eosin stain, original magnification × 100)*

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Sigmoidoscopy and multiple biopsies of the rectal stump revealed no abnormality, but colonoscopy through the stoma revealed numerous small polyps. Colectomy and ileorectal anastomosis were performed 5 months after the initial surgery; the colectomy specimen contained approximately 600 visible adenomas about 1 mm in size, and six larger polyps in the caecum and transverse colon. A cuff of rectum resected at the time was both macroscopically and microscopically normal. The patient's father had died aged 57 years and was known to have had an abdominoperineal resection of the rectum 5 years earlier for a carcinoma, but no other family members have been identified with colorectal tumours. DNA analysis of blood from the patient was uninformative in the absence of other known family members with FAP and there were no areas of congenital hypertrophy of the retinal pigment epithelium on indirect fundoscopy.

Patient 2

A 27-year-old mildly mentally retarded man presented with an iron deficiency anaemia and positive faecal occult bloods. Upper gastrointestinal endoscopy demonstrated two severely dysplastic duodenal adenomas of maximum diameters 2 and 3 cm. The patient had two epidermoid cysts on his lower limbs but rigid sigmoidoscopy revealed no abnormality in the rectum or lower sigmoid colon. The duodenal adenomas were resected locally with a full thickness of the duodenal wall resulting in a good postoperative recovery, although the patient remained anaemic despite oral iron therapy. A second gastroscopy showed no recurrent adenomas, but numerous right-sided colonic polyps were seen on colonoscopy. Indirect fundoscopy was then performed and showed multiple areas of congenital hypertrophy of the retinal pigment epithelium. Mandibular osteomas were also found on an orthopantomogram of the mandible. Cytogenetic studies showed a deletion in the long arm of chromosome 5 involving the site of the FAP gene at q22. The patient's mother had died at an early age from a subarachnoid haemorrhage and his father could not be traced. One maternal aunt was found with the same chromosomal abnormality and colonic polyposis.

Colectomy and ileorectal anastomosis were performed in this patient 6 months after the original surgery. The colectomy specimen showed approximately 100 predominantly right-sided polyps and a macroscopically normal descending and sigmoid colon. Microscopy of the 'normal' sigmoid mucosa, however, showed microadenomas similar to those found in case 1.

Discussion

Screening for FAP has most commonly been performed by means of rigid sigmoidoscopy[1], but the detection of congenital hypertrophy of the retinal pigment epithelium can be diagnostic[3] and analysis of DNA from blood samples is also useful in informative families. Correlation of these findings can usually accurately predict the likelihood of members of known FAP families carrying the affected gene[4]. Large bowel endoscopy is, however, still necessary to detect colorectal polyps, and rigid sigmoidoscopy remains a simple and practicable screening test.

DNA studies, pedigree analysis and the presence of congenital hypertrophy of the retinal pigment epithelium make it possible to identify most gene carriers in the presence of an endoscopically normal rectum. It has been suggested that rectal sparing never occurs in FAP in the presence of large adenomas or carcinomas[1,7], and that rigid sigmoidoscopy is adequate as the sole method of screening. Others[5,8] have reported the absence of rectal polyps and more recently Perry *et al.*[6] reported a colonic cancer in an FAP patient with no rectal polyps. The two cases reported here provide additional evidence of the necessity for flexible sigmoidoscopy to detect some cases of FAP. The value of this examination may be enhanced by multiple biopsies to detect microadenomas in the colonic mucosa.

The significance of microadenomas in FAP has only recently been appreciated; unicryptal and oligocryptal adenomas are particularly characteristic[7]. Adenomas in FAP are thought to start as dysplasia in a single cell or small group of cells in a crypt[7]. Electron microscopy demonstrates ultrastructural changes at this time[9,10] and small unicryptal and oligocryptal adenomas have been recognized on light microscopy. Tritiated thymidine labelling studies have demonstrated active division in the usually senescent superficial zones of the crypts[11]. This faster cell replication in a relatively quiescent mucosa results in localized overgrowth and leads to polyp development[12].

The practice of examining random biopsies of rectal and sigmoid mucosa has not been routine in screening for FAP. Nevertheless, these two cases demonstrate that florid polyposis and colonic carcinoma can coexist in FAP with a macroscopically and microscopically normal rectum. Total reliance on rigid sigmoidoscopy as an endoscopic investigation is therefore inappropriate. The use of a flexible endoscope and multiple biopsies to detect microadenomas may prove valuable in selected patients, particularly when other indicators such as congenital hypertrophy of the retinal pigment epithelium, DNA analysis and pedigree analysis predict gene carriage.

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References

1. Bulow S. Familial polyposis coli. *Dan Med Bull* 1987; **34**: 1–15.
2. Houlston R, Slack J, Murday V. Risk estimates for screening adenomatous polyposis coli. *Lancet* 1990; **i**: 484.
3. Chapman PD, Church W, Burn J, Gunn A. Congenital hypertrophy of retinal pigment epithelium: a sign of familial adenomatous polyposis. *Br Med J* 1989; **298**: 353–4.
4. Burn J, Chapman PD, Delhanty J *et al.* The UK Northern region genetic register for familial adenomatous polyposis: use of age of onset, congenital hypertrophy of the retinal pigment epithelium, and DNA markers in risk calculations. *J Med Genet* 1991; **28**: 289–96.
5. Moertel CG, Hill JR, Adson MA. Surgical management of multiple polyposis. *Arch Surg* 1970; **100**: 521–7.
6. Perry RE, Christensen MA, Thorson AG, Williams T. Familial polyposis: colon cancer in the absence of rectal polyps. *Br J Surg* 1989; **76**: 744–54.
7. Bussey HJR. Familial polyposis coli. *Pathol Annu* 1979; **14**: 61–81.
8. Schaupp WC, Volpe PA. Management of diffuse colonic polyposis. *Am J Surg* 1972; **124**: 218–22.
9. Dawson PA, Filipe MI, Bussey HJR. Ultrastructural features of the colonic epithelium in familial polyposis coli. *Histopathology* 1977; **1**: 105–13.
10. Mughal S, Filipe MI. Ultrastructural study of the normal mucosa-adenoma-cancer sequence in the development of familial polyposis coli. *J Natl Cancer Inst* 1978; **60**: 753–69.
11. Deschner EE, Lipkin M. Study of human rectal epithelial cells in vitro. III. RNA, protein and DNA synthesis in polyps and adjacent mucosa. *J Natl Cancer Inst* 1970; **44**: 175–85.
12. Lane N, Lev R. Observations on the origin of adenomatous epithelium of the colon. *Cancer* 1963, **16**: 751–64.

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Effects of different lipid emulsions on lymphocyte function during total parenteral nutrition

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A prospective randomized study of the immunological effects of three total parenteral nutrition (TPN) regimens in patients undergoing preoperative parenteral nutrition was conducted. In one regimen the calories were derived solely from glucose. The others were identical except that 50 per cent of the calories were provided as lipid emulsion, in one as long-chain triglycerides (LCT) only while the other contained half the fat as medium-chain triglycerides (MCT) and half as LCT (MCT/LCT). Natural killer (NK) activity and lymphokine-activated killer (LAK) activity were significantly higher after TPN with the MCT/LCT solution. A significant fall in LAK activity occurred after TPN with the LCT solution. The interleukin 2 content in supernatants from activated T lymphocytes was significantly higher after TPN with the LCT-containing solution. Solutions containing LCT and those containing MCT perturb cytokine interactions, but this is less with MCT-containing solutions, which may augment certain responses. These observations may have implications for the design of TPN regimens.

Lipid emulsions are an integral component of total parenteral nutrition (TPN) regimens[1,2]. It has been suggested that the most commonly employed lipid emulsions possess immunosuppressive properties which may have adverse long-term or short-term consequences[3,4]. Patients with malignant disease undergoing TPN may be more susceptible to sepsis[5] and may experience a shorter survival time and increased recurrence rates than those who do not receive intravenous nutrition[6,7].

Objective scientific support for these observations has, until recently, been unsatisfactory. A series of *in vivo* and *in vitro* studies[8–10] has established that standard lipid emulsions consisting predominantly of triglycerides containing long-chain triglycerides (LCT) (mainly unsaturated fatty acids in the form of oleic and linoleic acids) perturb those immune responses based on the interaction of the lymphokine interleukin 2 (IL-2) with its receptor on the lymphocyte surface. This is an appropriate model for the study of many clinically employed reagents on the immune response because (1) it is a reaction that is central to the generation of most types of immune response and (2) it is a simple, well characterized model which reflects many of the receptor–ligand interactions in the cascade of events that culminates in an effective immune response.

We have recently shown[10] *in vitro* that pharmacological concentrations of lipid emulsions containing only LCT are potently suppressive of IL-2-mediated responses whereas mixed lipid emulsions which provide 50 per cent of their calories as saturated medium-chain triglycerides (MCT) exert a significantly less suppressive influence on IL-2-mediated reactions. This report describes the findings in a prospective study of the *in vivo* immunological effects of TPN containing either no lipid solution or one containing an equicaloric volume of one of the two forms of lipid emulsion available (LCT exclusively or one in which 50 per cent of the triglyceride is provided as LCT and 50 per cent as MCT).

Patients and methods

Studies were undertaken on 33 patients with gastrointestinal cancer, most of whom were considered to be suitable candidates for 7 days of preoperative intravenous nutrition because of biochemical evidence of malnutrition (serum albumin $<32\ \mathrm{g\,dl^{-1}}$ or plasma transferrin $<2{\cdot}0\ \mathrm{g\,dl^{-1}}$) or clinical/anthropometric data indicating a loss of recall body-weight of 15 per cent or more. Patient details are shown in *Table 1*. All patients were randomly selected to receive one of three TPN regimens (*Table 1*).

Regimen A ($n=9$) consisted of purely carbohydrate-based TPN containing 0·3 gN $\mathrm{kg^{-1}\ day^{-1}}$ as a crystalline amino acid solution (Aminoplex 12®, Geistlich Sons Ltd., Chester, UK) and a calorie intake of 1·5 Er (estimated value of resting metabolic expenditure) kcal $\mathrm{day^{-1}}$ (Glucoplex®, Geistlich Sons Ltd.) as previously described[8].

Regimen B ($n=12$) was equicaloric and equinitrogenous with regimen A except that 50 per cent of the calories were provided as a lipid emulsion in which the calories were triglycerides containing only long-chain fatty acids (LCT; Intralipid 20 per cent®, Kabi, Bourne End, UK).

Regimen C ($n=12$) was equicaloric and equinitrogenous with regimens A and B except that 50 per cent of the calories were provided as an emulsion containing triglycerides of which half were composed of MCT and half were LCT (Lipofundin MCT/LCT 20 per cent®, B. Braun Medical Ltd., Aylesbury, UK). Immunological studies were performed on the day of initiation of TPN with the randomized regimen and repeated after 7 days of TPN.

Table 1 *Clinical data on 33 patients studied*

	Regimen A (no lipid) ($n=9$)	Regimen B (LCT) ($n=12$)	Regimen C (MCT/LCT) ($n=12$)
Mean(s.d.) age (years)	65(6)	71(9)	61(8)
Sex ratio (M:F)	4:5	8:4	6:6
Tumour type			
Oesophageal	1	1	1
Gastric	2	2	2
Colorectal	6	9	9
Criteria for malnutrition			
> 15 per cent loss of recall body-weight	2	3	4
Plasma transferrin $<2{\cdot}0\ \mathrm{g\,dl^{-1}}$	4	6	5
Serum albumin $<32\ \mathrm{g\,dl^{-1}}$	6	5	6
No. with no clinical or biochemical evidence of malnutrition	3	2	3

LCT, long-chain triglycerides; MCT, medium-chain triglycerides

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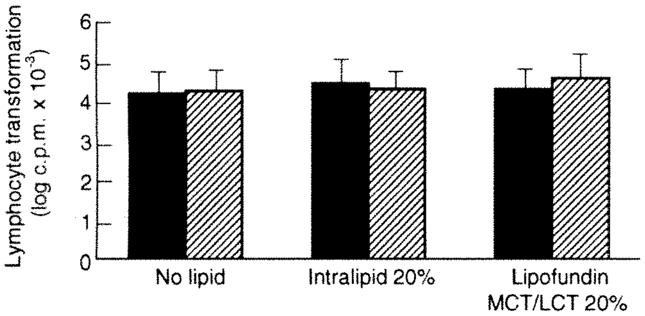

Figure 1 *Changes in lectin (concanavalin A)-activated lymphocyte transformation before (■) and 7 days after (▨) total parenteral nutrition (TPN) with each of the three TPN regimens. Histograms denote mean(s.e.m.) of log-transformed data. MCT/LCT, medium-chain triglycerides/long-chain triglycerides*

Immunological studies

Immunological studies were conducted on freshly isolated peripheral blood lymphocytes according to previously described methods[8]. Two assays of T cell function and two assays of lymphocytotoxicity were quantified, all of which are determined by IL-2 receptor–ligand interactions *in vitro* or *in vivo*.

T cell function: (a) Lymphocyte transformation in response to the T cell lectin concanavalin A. Concanavalin A-activated lymphocytes (2×10^6 ml^{-1}) were cultured in RPMI medium containing 10 per cent fetal calf serum in flat-bottomed microtitre trays in a total volume of 200 μl per well as previously described[8]. Parallel control wells contained no concanavalin A. The cultures were incubated at 37°C in a humidified atmosphere for 24 h at which time 100 μl supernatant was removed from each concanavalin A-activated well, pooled and stored at −70°C for subsequent batch analysis for IL-2 content. Each well was reconstituted with 100 μl fresh medium containing 1 μCi [^{3}H]thymidine. After a further 18 h incubation the wells were harvested on to filter paper discs and the radioactivity incorporated into DNA was measured by liquid scintillation counting.

T cell function: (b) IL-2 production by concanavalin A-activated lymphocytes. The supernatants obtained as described above were assayed for IL-2 content using the CTLL-2-based IL-2 bioassay as previously described[11]. From the incorporation of [^{3}H]thymidine into the CTLL-2 cells in duplicate wells at each dilution of experimental supernatant, a log dilution curve was constructed and the amount of IL-2 present in the supernatant in units per millilitre was calculated by probit-analysis by comparison with the curve obtained for doubling dilutions of a known standard of recombinant IL-2.

Lymphocytotoxic function: (a) Spontaneous natural killer (NK) activity. The NK activity of freshly isolated peripheral blood lymphocytes was measured using the K562 erythroleukaemic cell line as a target in a 4-h ^{51}chromium release assay as previously described[9,10]. The amount of specific ^{51}chromium release (specific cytotoxicity) at each effector:target cell ratio was then calculated according to the formula:

$$\text{Percentage of specific } ^{51}\text{chromium release} = \frac{\text{Experimental} - \text{spontaneous release}}{\text{Maximal} - \text{spontaneous release}} \times 100$$

The data for all effector:target cell ratios were converted to lytic units for that particular population of peripheral blood lymphocytes using the recently described area-under-the-curve method[12].

Lymphocytotoxic function: (b) Lymphokine-activated killer (LAK) cell activity. Fresh peripheral blood lymphocytes were cultured for 4 days at a concentration of 5×10^6 ml^{-1} in RPMI 1640/10 per cent fetal calf serum medium containing 1000 units ml^{-1} recombinant IL-2. At the end of this period the cells were harvested and used as effector cells in a ^{51}chromium release assay as described above but using the NK-resistant cell DAUDI as a target. Specific ^{51}chromium release and lytic units were calculated as described for the NK cell assay.

Statistical analyses

Logarithmic transformation of the data rendered them parametric, and statistical analysis used the STATISTIX program (Analytical Software, St. Paul, Minnesota, USA) on an IBM computer (Armonk, New York, USA). Analysis of variance was performed on the immunological data obtained before TPN to determine whether there was any significant difference between the three groups because of the known effects of malnutrition on lymphocyte function. Data obtained before and after TPN with treatment groups was analysed using the paired *t* test. *P* values of less than 5 per cent were considered to be statistically significant. A relatively small change in the logarithmic data in the figures represents a considerable change in the untransformed data.

Results

T lymphocyte function

All three treatment groups had identical lymphocyte [^{3}H]-thymidine uptake (stimulated and unstimulated) before TPN ($F = 1{\cdot}3$ and $F = 0{\cdot}3$ respectively, $P =$ n.s.). None of the TPN regimens had any effect on the spontaneous [^{3}H]thymidine uptake by unstimulated lymphocytes (data not shown). TPN had no significant impact on lectin-induced lymphocyte transformation in group A (no lipid) or group B (LCT). There was an increase in lymphocyte transformation in patients of group C who received TPN containing the MCT/LCT 20 per cent solution (MCT/LCT) ($t = 2{\cdot}15$, $P = 0{\cdot}05$) (*Figure 1*).

IL-2 release in response to lectin activation was similar in all three groups before TPN ($F = 1{\cdot}65$, $P = 0{\cdot}216$). The IL-2 content of supernatants from lectin-activated lymphocytes was significantly diminished following 7 days of lipid-free TPN ($t = 2{\cdot}9$, $P < 0{\cdot}05$) and was significantly augmented after 7 days of TPN containing only LCT as the non-glucose calorie source ($t = 4{\cdot}6$, $P < 0{\cdot}01$). In contrast there was no significant change in supernatant IL-2 content before and after TPN with the regimen which included 50 per cent of the calorie source as MCT/LCT (group C) (*Figure 2*).

Lymphocyte-mediated cytotoxicity

NK cell activity was similar in all three groups before TPN ($F = 1{\cdot}11$, $P = 0{\cdot}32$). There was no significant change in spontaneous NK cell activity before and after TPN in either group A (no lipid) or group B (LCT). Incorporation of MCT/LCT into the TPN regimen was accompanied by significant augmentation of spontaneous NK cell activity ($t = 3{\cdot}51$, $P < 0{\cdot}01$) (*Figure 3*).

LAK cell generation from the peripheral blood lymphocytes of all three groups was similar before the institution of TPN ($F = 0{\cdot}19$, $P = 0{\cdot}83$). After 7 days of TPN, the capacity to generate LAK cells from lymphocytes in response to activation with IL-2 was diminished in both groups A and B, but only in group B (LCT) did this reach statistical significance ($t = 7{\cdot}62$, $P < 0{\cdot}001$). In contrast, LAK cell induction was significantly

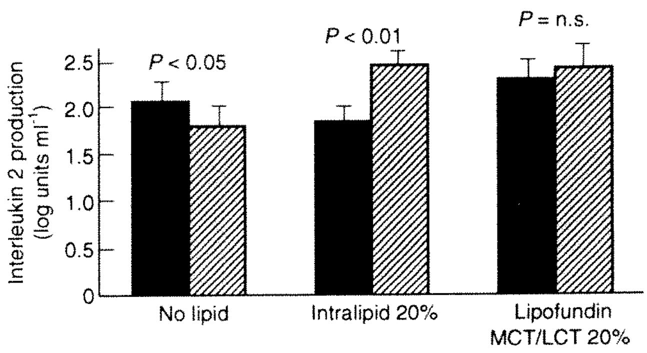

Figure 2 *Changes in interleukin 2 content of supernatants from lectin-activated lymphocytes before (■) and 7 days after (▨) total parenteral nutrition (TPN) with each of the three TPN regimens. Histograms denote mean(s.e.m.) of log-transformed data. MCT/LCT, medium-chain triglycerides/long-chain triglycerides*

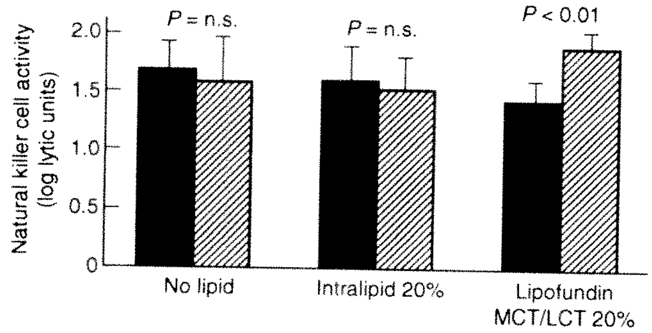

Figure 3 *Changes in spontaneous natural killer cell activity before* (■) *and 7 days after* (▨) *total parenteral nutrition (TPN) with each of the three TPN regimens. Histograms denote mean(s.e.m.) of log-transformed data. MCT/LCT, medium-chain triglycerides/long-chain triglycerides*

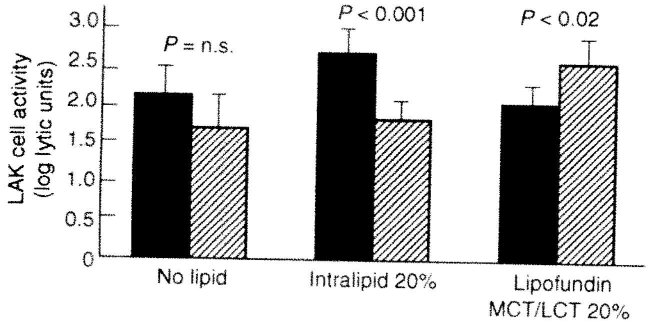

Figure 4 *Changes in the capacity to induce lymphokine-activated killer (LAK) cells in response to interleukin 2 before* (■) *and 7 days after* (▨) *total parenteral nutrition (TPN) with each of the three TPN regimens. Histograms denote mean(s.e.m.) of log-transformed data. MCT/LCT, medium-chain triglycerides/long-chain triglycerides*

augmented after 7 days of TPN with the regimen containing MCT/LCT (group C) ($t = 2{\cdot}49$, $P < 0{\cdot}02$).

Discussion

This investigation shows that the administration of TPN with glucose as the energy source has insignificant effects on most aspects of cellular immunity and confirms data from two previous studies which reported an increase in the IL-2 content of activated lymphocytes from patients who had received a lipid emulsion containing only LCT (Intralipid 20 per cent)[8,9]. Emulsions containing only LCT probably interfere with the binding of IL-2 to its receptor[10] and there is more free IL-2 in the supernatants of activated lymphocytes from patients so treated. The interference with IL-2 binding to its receptor has a potent immunosuppressive effect which influences a number of other components of the immune response which are pertinent to the development of sepsis and of anti-tumour responses. Solely glucose-based TPN increases plasma free fatty acids[13] and the absence of altered immune function in patients receiving glucose alone suggests that the relationship between exogenous LCT and the immune parameters measured may be complex.

The physiological control of NK cell activity is influenced by endogenously produced IL-2. In this study NK cell activity fell in the groups receiving no lipid or the LCT-alone solution. Neither of these changes was significant. After 7 days of TPN, NK cell activity increased significantly in the group receiving the mixed MCT/LCT emulsion. The IL-2 content of supernatants from cells obtained from the patients who received no lipid was diminished, suggesting either a failure of production or a failure of binding of IL-2. This may be an inevitable event in suboptimally fed patients. Since LCT-containing lipid solutions appear to impair IL-2 receptor–ligand binding, these data suggest that the administration of a mixed MCT/LCT solution provides a more appropriate environment for optimal IL-2/NK cell reactions to occur. *In vitro* studies suggested that this was partly attributable to the proportionally lower content of long-chain fatty acid-containing triglyceride in the MCT/LCT solution than in the LCT-alone solution. A dose–response relationship existed between immunosuppression and LCT concentration. This may be an over-simplification because spontaneous NK cell activity was not impaired (and was apparently augmented) during TPN with the MCT/LCT solution. A recent phenotypic analysis of changes in NK cell activity in patients randomized to receive either the LCT or MCT/LCT lipid emulsion reported diminished T cell and NK cell numbers in patients in the former group and not the latter[14].

The hypothesis that administration of MCT/LCT emulsions *in vivo* provides a relatively non-suppressive environment compared with the administration of LCT alone is supported by the IL-2-induced LAK cell generation in the present study. NK cells are the precursors of LAK cells and the changes in LAK cell induction in the three groups partially parallels the effects of these TPN regimens on spontaneous NK cell activity. In the LCT group there was a fall in LAK cell induction in keeping with the hypothesis that LCT-containing emulsions interfere with IL-2–receptor interactions. In the group of patients who received the MCT/LCT solution there was no suppression of LAK cell induction and the significant rise in this parameter suggests a more complex influence of lipid solutions on leucocyte function.

These data are consistent with *in vitro* studies in which LCT solutions were found to have potent suppressive effects on the consequences of IL-2 binding to its receptor. The effects of MCT/LCT on these interactions were much less marked[10]. There is no evidence to suggest that these effects have any significant clinical consequences in the majority of malnourished patients who might be considered to be candidates for TPN. Two randomized clinical studies of lipid-based TPN as an adjunct to cancer surgery or chemotherapy have shown the TPN group to fare less well than the control, non-fed group in terms of long-term cancer survival rates[6,7]. Most comparisons of lipid-based TPN with glucose-based TPN have concentrated on the metabolic consequences, with no examination of the prevalence of sepsis or of long-term survival rates from cancer therapies. The IL-2 receptor–ligand interaction is central to many components of the immune response to sepsis and the control of malignant progression. It serves as a model for the interaction of many other cytokines with their respective receptors on lymphoreticular cells with important functions in sepsis and malignant disease. Although IL-2 and T cell function are considered to be central to many components of the immune response, those molecular interactions of immediate relevance to the development of sepsis in patients who might be candidates for TPN tend to be somewhat downstream of IL-2 and its receptors. Nevertheless the principles are identical in that, for example, the full maturation of functionally active monocytes and polymorphonuclear leucocytes is dependent on the elaboration and binding to their precursors of activating growth factors such as monocyte-colony stimulating factor (M-CSF) or granulocyte-colony stimulating factor (G-CSF). Factors such as exogenous LCT, which modify the interactions between IL-2 and its cellular receptor, may have an impact on the binding and cellular responses of other cytokines with their target cells which are already impaired by trauma[15]. Individual long-chain fatty acids such as the C18 fatty acid, stearic acid, selectively inhibit T cell function but leave B cell function intact[16,17]. Such mechanisms may explain some of the present observations assuming that clinically administered LCT are subjected to the enzymatic effects of serum or cell-bound lipase which releases long-chain fatty acids from these triglycerides.

There are no prospective studies which suggest that lipid emulsions adversely influence the prevalence of infection in patients who require TPN. Modification of the immune response to infection may tilt the balance of events against the patient's survival, and the administration of inappropriate intravenous lipid emulsions may be one such modification[18]. The use of lipid as an intravenous energy source is indispensible. The design of lipid emulsions which do not possess immunologically detrimental properties may be a contribution to the diminution of the mortality rate from conditions requiring intravenous nutritional support.

References

1. Macfie J. Towards cheaper intravenous nutrition. *Br Med J* 1986; **292**: 107–10.
2. Tweedle DEF. The use of fat emulsions in parenteral nutrition. In: Johnston IDA, ed. *Advances in Parenteral Nutrition.* Lancaster: MTP Press, 1978: 165–77.
3. Fischer CW, Hunter KW, Wilson SR, Mease AD. Diminished bacterial defences with Intralipid. *Lancet* 1980; **ii**: 819–20.
4. Freeman J, Goldman DA, Smith NE *et al.* Association of intravenous lipid emulsion and coagulase-negative staphylococcal bacteraemia in neonatal intensive care units. *N Engl J Med* 1990; **323**: 301–8.
5. Klein S, Simes J, Blackburn GL. Total parenteral nutrition and cancer clinical trials. *Cancer* 1986; **58**: 1378–86.
6. Nixon DW, Moffitt S, Lawson DH *et al.* Total parenteral nutrition as an adjunct to chemotherapy of metastatic colorectal cancer. *Cancer Treat Rep* 1981; **65**(Suppl 5): 121–8.
7. Shamberger RC, Brennan MF, Goodgame JT *et al.* A prospective randomised study of adjuvant parenteral nutrition in the treatment of sarcomas. *Surgery* 1984; **96**: 1–12.
8. Monson JRT, Ramsden CW, MacFie J, Brennan TG, Guillou PJ. Immunorestorative effects of lipid emulsion during total parenteral nutrition. *Br J Surg* 1986; **73**: 843–6.
9. Monson JRT, Sedman PC, Ramsden CW, Brennan TG, Guillou PJ. Total parenteral nutrition adversely influences tumour-directed cellular cytotoxic responses in patients with gastrointestinal cancer. *Eur J Surg Oncol* 1988; **14**: 435–43.
10. Sedman PC, Ramsden CW, Brennan TG, Guillou PJ. Pharmacological concentrations of lipid emulsions inhibit interleukin-2 dependent lymphocyte responses *in vitro. J Parenter Enteral Nutr* 1990; **14**: 12–17.
11. Monson JRT, Ramsden CW, Guillou PJ. Decreased interleukin-2 production in patients with gastrointestinal cancer. *Br J Surg* 1986; **73**: 485–6.
12. Dye JF, Somers SS, Guillou PJ. Simplified quantitation of cytotoxicity by integration of specific lysis against effector cell concentration at a constant target cell concentration and measuring the area under the curve. *J Immunol Methods* 1991; **138**: 1–13.
13. Nordenstrom J, Askanazi J, Elwyn DH *et al.* Nitrogen balance during total parenteral nutrition: glucose v. fat. *Surgery* 1983; **197**: 27–33.
14. Gogos CA, Kalfarentzos FE, Zoumbos NC. Effect of different types of total parenteral nutrition on T-lymphocyte subpopulations and NK cells. *Am J Clin Nutr* 1990; **51**: 119–22.
15. Moore FA, Peterson VM, Moore EE, Rundus CR, Poggetti R. Inadequate granulopoiesis after major torso trauma: a haemopoietic regulatory paradox. *Surgery* 1990; **108**: 667–75.
16. Tebbey PW, Buttke TM. Molecular basis for the immunosuppressive action of stearic acid on T-cells. *Immunology* 1990; **70**: 379–84.
17. Buttke TM, van Cleave S, Steelman L, McCubrey JA. Absence of unsaturated fatty acid synthesis in murine T lymphocytes. *Proc Natl Acad Sci USA* 1989; **86**: 6133–5.
18. Venus B, Smith KA, Patel C, Sandoval E. Hemodynamic and gas exchange alterations during Intralipid infusion in patients with adult respiratory distress syndrome. *Chest* 1989; **95**: 1278–81.

Paper accepted 8 July 1991

Correspondence

Laparoscopic cholecystectomy: a cautionary note

Sir

The fulsome welcome laparoscopic cholecystectomy has received from many of the leading journals in the British Isles and North America[1–5] has had the effect, intentional or otherwise, of pushing general surgeons into the widespread adoption of this operation with often barely adequate training in laparoscopic techniques. It is already being practised in most district and community hospitals in this country. As a surgeon not yet convinced about its safety or efficacy, I was impressed by the wise caution and common sense displayed by Paterson-Brown *et al.* in their leading article (*Br J Surg* 1991; **78**: 131–2). However, the clear message that comes from McEntee *et al.* in their leading article (*Br J Surg* 1991; **78**: 385–6) is that laparoscopic cholecystectomy has already passed the test. That assertion in itself takes a certain amount of fortitude. Subsequently to infer, albeit as a moot point, that routine peroperative cholangiography and clearance of the common bile duct (CBD) of all stones may no longer be a prerequisite for safe biliary surgery is surely injudicious and premature.

Seven hundred and twenty-one patients underwent traditional open operation for non-malignant biliary tract disease in our two-surgeon unit between January 1985 and December 1990. The mean(s.d.) age of the patients was 49(16) years, and 25 per cent of them were over 65 years old. Six hundred and thirty had a simple cholecystectomy only, and 91 had in addition a CBD exploration. Thirteen patients had an emergency cholecystectomy (within 24 h of admission), 166 had an urgent cholecystectomy (within 5 days) and 542 had an elective operation. Simple cholecystectomy operations lasted 85(25) min. Operative cholangiograms were performed in 92 per cent of cases. The postoperative length of stay for simple cholecystectomy was 5·7(4·2) days. There were no deaths. The procedure-related morbidity for simple cholecystectomy was 2·4 per cent, the vast majority being due to sepsis. No bile duct injuries occurred.

On the basis of these results it is difficult to make a convincing case for changing to laparoscopic cholecystectomy. The initial reports and editorial comment on laparoscopic cholecystectomy suggest it is a safe operation[1–5]. This has been responsible for the remarkable speed of its acceptance among general surgeons. There is now some disquiet that this uncritical acclaim is wide of the mark. Occasional reports of serious complications[6–8] and more measured comment[4,9] have appeared in the literature but less than one might expect for a new technique being robustly applied by a large proportion of general surgeons. To suggest that what little morbidity there is is largely related to a learning curve is not borne out by the consistent morbidity rates associated with many interventional endoscopic procedures that have been in use for several years[10–12]. More widespread information on complication rates of this new procedure is necessary, and judgement should be deferred for the moment.

The case for a prospective controlled comparison of laparoscopic *versus* open cholecystectomy seems very strong. The leaders of our specialty should see that this is done now when it is still feasible rather than have it demanded of us later, as has happened to the urologists in relation to prostatectomy.

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1. Wastell C. Laparoscopic cholecystectomy. *Br Med J* 1991; **302**: 303–4.
2. Cuschieri A. Laparoscopic cholecystectomy. *Br J Hosp Med* 1991; **45**: 65.
3. Olsen DO. Laparoscopic cholecystectomy. *Am J Surg* 1991; **161**: 339–44.
4. Paterson-Brown S, Garden OJ, Carter DC. Laparoscopic cholecystectomy. *Br J Surg* 1991; **78**: 131–2.
5. McEntee G, Grace PA, Bouchier-Hayes D. Laparoscopic cholecystectomy and the common bile duct. *Br J Surg* 1991; **78**: 385–6.
6. Greville AC, Clements EAF, Erwin DC, McMillin DL, Wellwood JM. Pulmonary air embolism during laparoscopic laser cholecystectomy. *Anaesthesia* 1991; **46**: 113–14.
7. Greville AC, Clements EAF. Anaesthesia for laparoscopic cholecystectomy using the Nd:YAG laser. *Anaesthesia* 1990; **45**: 944–5.
8. Joshi P, Mahoney A, Soni NC. Other implications of laser laparoscopic cholecystectomy. *Anaesthesia* 1991; **46**, 318 (Letter).
9. Curtis SC, Russell RCG. Laparoscopic cholecystectomy. *Br Med J* 1991; **302**: 594 (Letter).
10. Lambert ME, Betts CD, Hill J, Faragher EB, Martin DF, Tweedle DEF. Endoscopic sphincterotomy: the whole truth. *Br J Surg* 1991; **78**: 473–6.
11. Tilanus HW, Bossuyt P, Schattenkerk ME, Obertop H. Treatment of oesophageal perforation: a multivariate analysis. *Br J Surg* 1991; **78**: 582–5.
12. Hall C, Dorricott NJ, Donovan IA, Neoptolemos JP. Colon perforation during colonoscopy: surgical *versus* conservative management. *Br J Surg* 1991; **78**: 542–4.

Influence of cholecystectomy on symptoms

Sir

We were interested to read the excellent study of Bates *et al.* (*Br J Surg* 1991; **78**: 964–7) looking at symptoms in patients undergoing cholecystectomy. We have undertaken a similar study of 75 patients undergoing cholecystectomy in our hospital, with follow-up at 1 year.

Seventy-three per cent of patients were cured of pain. Of those who had the symptom preoperatively, 72 per cent were cured of fatty intolerance, 64 per cent of nausea, 57 per cent of flatulence, 57 per cent of indigestion and 49 per cent of distension. It is not possible to deduce such 'cure rates' from the data presented by Bates *et al.*, as crude preoperative and postoperative frequencies ignore those who develop a symptom during follow-up. We found that a third of patients developed at least one new symptom during the year after operation. A four-grade scale was used to gauge patient satisfaction, and 77 per cent of patients graded themselves either completely or well satisfied.

We would agree with the authors' conclusion that prediction of symptomatic relief after cholecystectomy is difficult. However, we now have data to present to patients to indicate the likelihood of their symptoms being relieved in our hands. We hope this will further improve the satisfaction felt by our patients.

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Effects of relief of biliary obstruction on mononuclear phagocyte system function and cell mediated immunity

Sir

I read with interest the paper by Megison *et al.* (*Br J Surg* 1991; **78**: 568–71). It is an experimental paper of high interest, which confirms some of the clinical findings that we and other authors have recently published.

We have previously shown a relationship between the presence of jaundice and altered cellular immunity, irrespective of the type of jaundice, whether benign or malignant[1,2]. In a further study of 25 patients we showed recovery of cellular immunity once jaundice was relieved[3]. As in the present work in rats, reversion from the anergic state to the immune-competent state develops rapidly once jaundice is relieved. These findings suggest that an adequate internal biliary drainage procedure should benefit jaundiced patients by restoring cellular immunity to normal, thereby limiting sepsis at the time of definitive surgery.

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1. Cainzos M, Potel J, Puente JL. Anergy in jaundiced patients. *Br J Surg* 1988; **75**: 147–9.
2. Cainzos M, Potel J, Puente JL. Anergy in patients with biliary lithiasis. *Br J Surg* 1989; **76**: 169–72.
3. Cainzos M, Alcalde JA, Potel J, Puente JL. Variation in the cellular immune response as a function of total bilirubin. *Surg Res Comm* 1990; **7**: 285–99.

Use of a mètal cannula for peroperative cholangiography

Sir

I was pleased to read the surgical workshop concerning the use of a metal cannula for operative cholangiography (*Br J Surg* 1991; **78**: 426). As a junior surgical trainee, I was taught to use many of the alternative devices listed in the article. While each of these served their purpose, I found the 'Gourevitch' cannula (as it was known) by far the easiest to use. I have come across it only at one hospital, and have found no other knowledge of its existence. The article is to be welcomed as a means of increasing the awareness of this useful instrument.

On a simple matter of detail, I was taught to use the cannula with the 20-ml syringe attached directly to it. The syringe provided a manageable 'handle' to manipulate the cannula into the cystic duct, and did not hamper the subsequent cholangiogram by its presence in the wound.

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Talc as a pleural sclerosant

Sir

I read with interest the paper by Hamed *et al.* comparing intrapleural bleomycin and talc in neoplastic pleural effusion[1]. I completely agree with the authors as to the superiority of talc over any other sclerosant and am not aware of any trials to the contrary in which talc and another substance have been directly compared. I have used talc as a sclerosant for almost 40 years and published the results of my first 30 patients with neoplastic pleural effusion in 1958[2]. I have had success with talc in patients where other sclerosants have failed. Success is even possible where incomplete lung expansion occurs as the space often fills with coagulum which scars and prevents recurrence of effusion.

As to the drawbacks to talc mentioned in the literature, one had to do with the instillation of talc by insufflation: apparently this was inconvenient and difficult. This can be obviated by suspending the talc in saline and instilling it much as any other liquid sclerosant. In fact, some hospitals in San Diego suspend under sterile conditions 10 g talc in 100 ml of saline in a 250-ml bottle. This can be used anywhere in the hospital, including the operating suite. Pain is the other drawback mentioned regarding the use of talc in neoplastic effusion. I have found that this is less than with spontaneous pneumothorax, perhaps because the pain nerve fibres were already maximally stimulated by the tumour. Post-instillation pain has been minimized since epidural analgesia became available. I have employed local anaesthetic for intubation and talc instillation in the operating suite, and had not used general anaesthesia even before epidural analgesia became popular.

I have not hesitated to use this sclerosant in old debilitated patients, but agree with the authors against its use where prognosis is less than 1 month. It can be used in non-neoplastic effusions and is the treatment of choice in chylothorax from whatever cause. The use of talc usually saves thoracotomy in this case. Again, I would like to congratulate the authors on their important observations, and hope my remarks might be helpful. The use of the talc suspension via intubation obviates the need for thoracoscopy as it simplifies the procedure without detracting from the almost uniformly good results.

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1. Hamed H, Fentiman IS, Chaudary MA, Rubens RD. Comparison of intracavitary bleomycin and talc for control of pleural effusions secondary to carcinoma of the breast. *Br J Surg* 1989; **76**: 1266–7.
2. Chambers JS. Palliative treatment of neoplastic pleural effusion with intercostal intubation and talc instillation. *Western J Surg Obstet Gynaecol* 1958; **66**: 26–8.

Surgical management of primary hyperhidrosis

Sir

I read with interest the recent article by Moran and Brady on surgical approaches for the treatment of primary hyperhidrosis (*Br J Surg* 1991; **78**: 279–83). I would like to point out that the dorsal midline approach of Cloward is still used by neurosurgeons, particularly in North America[1–3]. In fact, the two largest reported series in the literature (457 patients[4] and 440 patients[1]) are of patients with hyperhidrosis treated with sympathectomy via a dorsal midline approach.

At our institution we have treated 464 patients to date for primary palmar hyperhidrosis by a modification of this approach, which involves a posterior midline incision, with a bilateral third rib costotransversectomy allowing for a one-stage bilateral excision of the second thoracic sympathetic ganglion[1]. If axillary sweating is a prominent concurrent complaint, then both the T2 and T3 ganglia are removed. Ninety-four per cent of patients had long-term satisfaction with surgical results after a mean follow-up period of 6·5 years. Frank recurrent palmar sweating occurred in only three patients. The main complications were wound infection (2·5 per cent) and pneumothorax requiring chest tube insertion (< 1 per cent of patients). None of our patients developed Horner's syndrome. The mean duration of hospital stay in our last 100 patients has been 3·4 days.

We are satisfied that the dorsal midline approach remains an important and worthwhile alternative to the endoscopic thoracic, cervical and transaxillary approaches discussed in detail by Moran and Brady.

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1. Pillay PK, Awad IA, Little JR, Dohn DF, Bay JW. Upper thoracic sympathectomy for essential palmar hyperhydrosis: Cleveland Clinic experience with 440 cases. *Proceedings of the 39th Annual Meeting of the Congress of Neurological Surgeons*. Atlanta, Georgia, 1989: 217.
2. Pillay PK, Awad IA, Dohn DF. Upper thoracic sympathectomy by a posterior midline approach. In: Wilkins RH, Rengachary SS, eds. *Atlas of Neurosurgery*. Baltimore: Williams and Wilkins, 1991 (in press).
3. Hardy RW, Bay JW. Surgery of the sympathetic nervous system. In: Schmidek HH, Sweet WH, eds. *Operative Neurosurgical Techniques*. 2nd ed. Florida: Grune and Stratton, 1988: 1271–4.
4. Shih C, Wang Y. Thoracic sympathectomy for palmar hyperhydrosis: report of 457 cases. *Surg Neurol* 1978; **10**: 291–6.

Colon perforation during colonoscopy: surgical *versus* conservative management

Sir

We read with interest the recent article by Hall *et al.* (*Br J Surg* 1991; **78**: 542–4) concerning the incidence of colonic perforation during colonoscopy. In this paper the authors reviewed a large number of patients (17 500) who underwent colonoscopy and identified 15 of these who actually suffered a colonic perforation. Of these 15 only one was managed conservatively, and none of the patients suffered significant morbidity after treatment. In their discussion the authors review the data rationally and recommend that trials of conservative management may warrant more frequent consideration, but counter this with the argument that delaying surgery in some cases may lead to an irretrievable situation. They suggest all such perforations be discussed with a surgeon at an early stage. However, in the abstract published with this paper (similar to an abstract previously published in *Gut* in 1990[1]), the recommendation that more patients should be treated conservatively is stated without qualification and is not supported by the data presented in the paper.

The abstract is an important component of a paper and will be the only part read by many readers. In addition, it will be this that is retrieved by on-line computer searches which are becoming increasingly important in modern medicine. Therefore, it is vital that the abstract is a true reflection of the paper to which it relates. Unfortunately we do not feel that this is so in this case.

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1. Hall C, Dorricott NJ, Donovan IA, Neoptolemos JP. Colonoscopic perforation – are there too many laparotomies? *Gut* 1990; **31**: A605.

Authors' reply

Sir

Messrs Osborne and Stansby are correct in demanding that abstracts should accurately reflect the contents of the manuscript. It is, however, important to distinguish between the type of study that can by its design provide an incontrovertible answer and one that can not. Our study on the management of colonoscopic colonic perforation depends on relatively soft data. Any conclusions that can be drawn will also be 'soft'. Yet such a study can still be of value if the question being asked is important and there is no alternative way of providing an answer for the present.

The one patient in the study with a perforation managed conservatively had clear-cut peritonitis (temperature, 39°C; white cell count, 18×10^9/l; obvious air under the diaphragm; lower abdominal guarding and rebound tenderness). Three other patients who had a laparotomy in whom no perforation could be found, and had absence of soiling, could have been managed similarly in our opinion. Naturally we would welcome harder data to support such a general conclusion.

Letters to journals about articles should be accurate. In the abstract of the *British Journal of Surgery* paper we did not give 'the recommendation that more patients should be treated conservatively'; rather we 'recommended that patients who have had a good bowel preparation should be treated conservatively unless there is a large perforation or an underlying carcinoma'. Initial conservative management does not rule out subsequent operation.

A wise old chief once said that the important decisions are rarely black and white, for these are obvious; it is the grey areas in life that often demand the greatest skill. We hope that our paper has helped to make the decision-making process in colonoscopic colonic perforation, a very large 'grey' area, a little easier.

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Necrotizing fasciitis

Sir

The well presented series of cases by Asfer *et al.* (*Br J Surg* 1991; **78**: 838–40) prompts me to write. We have proposed an aetiological hypothesis based on a series of patients with necrotizing fasciitis of the scrotal and perineal areas[1]. In our series, an ischaemic watershed between superior and middle rectal arteries was present in each patient due either to previous surgery or to coexistent atheromatous disease, which may be secondary to diabetes mellitus. Superadded synergistic infection with anaerobic flora can then progress to necrosis. Knowledge of such a mechanism may be useful in designing a rational approach to treatment, e.g. hyperbaric oxygen and prostacyclin could conceivably be beneficial in addition to broad spectrum antibiotics and surgical debridement.

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1. Edmonson R, Banerjee AK, Rennie JA. Fournier's gangrene – a possible mechanism? *Br J Urol* 1991 (in press).

Angioplasty for mild intermittent claudication

Sir

The excellent précis by Whyman *et al.* (*Br J Surg* 1991; **78**: 643–5) on the current state of angioplasty for peripheral vascular disease was read with interest. From a radiologist's point of view perhaps the article could be criticised for being slightly over-cautious, but there is nothing with which to take issue. In particular, I agree that more trials are required, though randomized controlled trials in this condition are notoriously difficult to conduct due to disease pattern variations. Vascular surgeons should be aware that the Royal College of Radiologists is about to embark on a National Audit of Angioplasty which hopefully may answer some of the outstanding questions.

Collaboration between surgeons and radiologists in the collection of follow-up data, vital to the study, would greatly enhance the validity of such data.

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Infrainguinal bypass surgery

Sir

Budd *et al.* (*Br J Surg* 1990; **77**: 1382–7) present an extensive experience with infrainguinal bypass surgery for occlusive vascular disease. However, in stating that 'Overall, the results suggest that prosthetic grafts are a suitable alternative to autogenous vein when the distal anastomosis is above the knee', the authors draw conclusions that are not fully supported by the data that they present. Such errors are unfortunately common in the surgical literature[1].

Although they state that there was no difference in patency between vein and prosthesis above the knee, the data in *Table 3* show that the occlusion rate of prosthesis is approximately 50 per cent greater at 5 years (67 per cent *versus* 49 per cent 5-year patency). It is important not to confuse the failure to show a significant difference, which may be a Type II error[2], with evidence that no difference exists. Although identical patency is a possibility on the data that they present, it is also possible that the difference is much greater than was found, and confidence limits would have been helpful in interpretation. To demonstrate with statistical significance that no important difference exists would require a trial that is powerful enough to show the smallest difference that would be considered clinically significant.

The authors' own statistical analysis, using the proportional hazards method, suggests that graft material is one of four variables *independently* associated with graft occlusion, and that there were no interactions between the covariates. The implication of this is that their data are consistent with prosthetic grafts having the same proportionate increase in occlusion rate, irrespective of the level of distal anastomosis. This is clearly at odds with the conclusion that is drawn in the discussion and abstract.

The authors cite two other papers in support of their conclusions. The paper by Yeager *et al.*[3] includes only six above-knee grafts, which are not analysed separately. In the excellent randomized trial reported by Veith *et al.*[4] the results were similar to their own, demonstrating better patency for vein grafts above the knee (61 per cent *versus* 38 per cent at 4 years) which is not of statistical significance. If these papers reflect the true difference then, considering the difficulty in collecting a large number of patients with long-term follow-up, the failure to reach statistical significance is not surprising. However, the large number of papers that have demonstrated broadly similar results suggests that the difference is real[5].

There may be other possible reasons for using prosthesis in preference to vein. The value of preserving the vein for later surgery requires careful mathematical evaluation[5]. Shorter operating time, fewer complications or shorter hospital stay are other possible advantages, particularly with restrictions on theatre time and surgical beds. However, the authors present no evidence for these advantages, which would have to be carefully evaluated against the possible costs in terms of re-occlusions and re-operations.

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1. Evans M. Presentation of manuscripts for publication in The British Journal of Surgery. *Br J Surg* 1989; **76**: 1311–15.
2. Freiman JA, Chalmers TC, Smith H, Kuelber RR. The importance of beta, the type II error and sample size in the design and interpretation of the randomized control trial. *N Engl J Med* 1978; **299**: 690–4.
3. Yeager RA, Hobson RW, Jamil Z, Lynch TG, Lee BC, Jain K. Differential patency and limb salvage for polytetrafluoroethylene and autogenous saphenous vein in severe lower extremity ischemia. *Surgery* 1982; **9**: 99–103.
4. Veith FJ, Gupta SK, Ascer E *et al.* Six-year prospective multicenter randomized comparison of autologous saphenous vein and expanded polytetrafluoroethylene grafts in infrainguinal arterial reconstructions. *J Vasc Surg* 1986; **3**: 104–14.
5. Michaels JA. Choice of material for above-knee femoropopliteal bypass graft. *Br J Surg* 1989; **76**: 7–14.

Extended hepatectomy for hepatocellular carcinoma

Sir

I read with interest the article on extended hepatectomy for hepatocellular carcinoma by Al-Hadeedi *et al.* (*Br J Surg* 1990; **77**: 1247–50). I agree with their conclusion that extended hepatectomy is a worthwhile operation for large hepatocellular carcinoma (HCC) given careful patient selection. Al-Hadeedi *et al.* compared the rates of postoperative complication and survival for extended hepatectomy and for one of a lesser extent, showing the results to be essentially the same. However, I believe attention should be directed to the recurrence rate and surgical resection margin in the two groups.

Follow-up studies after hepatectomy for HCC have shown a high intrahepatic recurrence rate of 50 per cent or more[1–3]. The survival rate may differ between these procedures. This is because the volume of liver remnant is different in the extended and less extended hepatectomy groups. Alternatively, there may be a difference in the surgical margin[4]. With extended hepatectomy, the margin can be less than 1 cm whereas in hepatectomy of the lesser extent it can be more. Even if resection margins are initially sufficient, it is all too easy to stray closer to the tumour as resection proceeds[5]. Published results on liver transplantation for HCC are disappointing[6–8], although when transplantation has been done to treat end-stage cirrhosis with incidental malignancy the results have been better[6]. No study of liver resection *versus* liver transplantation as a treatment for HCC in the cirrhotic organ has been published. This problem may require a prospective trial.

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1. Lin TY, Lee CS, Chen KM, Chen CC. Role of surgery in the treatment of primary carcinoma of the liver: a 31-year experience. *Br J Surg* 1987; **74**: 839–42.
2. Kanematsu T, Matsumata T, Takenaka K, Yoshida Y, Higashi H, Sugmiachi K. Clinical management of recurrent hepatocellular carcinoma after primary resection. *Br J Surg* 1988; **75**: 203–6.
3. Nagao T, Inoue S, Yoshimi F *et al.* Postoperative recurrence of hepatocellular carcinoma. *Ann Surg* 1990; **211**: 28–33.
4. Yoshida Y, Kanematsu T, Matsumata T, Takenaka K, Sugimachi K. Surgical margin and recurrence after resection of hepatocellular carcinoma in patients with cirrhosis. Further evaluation of limited hepatic resection. *Ann Surg* 1989; **209**: 297–301.
5. Ezaki T, Stansby GP, Hobbs KEF. Letter to the Editor. *Cancer* 1990; **65**: 2101.
6. Iwatsuki S, Gordon RD, Show BW Jr, Starzl TE. Role of liver transplantation in cancer therapy. *Ann Surg* 1985; **202**: 401–7.
7. O'Grady JG, Polson RJ, Calne RY, Williams R. Liver transplantation for malignant disease: results in 93 consecutive patients. *Ann Surg* 1988; **207**: 373–9.
8. Ringe B, Wittekind C, Bechstein WO, Bunzendahl H, Pichlmayr R. The role of liver transplantation in hepatobiliary malignancy. A retrospective analysis of 95 patients with particular regard to tumour stage and recurrence. *Ann Surg* 1989; **209**: 88–98.

Influence of obstructive jaundice on the serum levels of sodium

Sir

Oms and colleagues (*Br J Surg* 1990; **77**: 752–5) report high levels of atrial natriuretic factor and reduced water and sodium intakes following common bile duct ligation in the rabbit. In a multivariate analysis of peroperative risk factors in patients undergoing cholecystectomy and common bile duct exploration, we have found lower serum levels of sodium in the presence of obstructive jaundice. Among 401 patients studied retrospectively, there were 101 with obstructive jaundice (caused by gallstones). Five of the 300 anicteric patients (1·7 per cent) had serum sodium levels below 134 mmol/l ($P < 0\cdot01$) as opposed to eight of the 101 icteric patients (7·9 per cent). There was no significant difference in serum potassium between the patients with and without obstructive jaundice (4·33 *versus* 4·38 mmol/l). These data support the results of Oms *et al.* concerning the influence of obstructive jaundice on the regulation of sodium levels. We found no indirect evidence of dehydration in the jaundiced patients. There were no significant differences in the haematocrit or body-weight (BROCCA index) between these two groups. A low serum sodium was not a significant predictor of postoperative complications.

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Notices and announcements

14–16 November 1991
10th Annual WBAMC Trauma Symposium
El Paso, Texas, USA
Information: Mrs Marty May, Trauma Service/SICU, Department of the Army, William Beaumont Army Medical Center, El Paso, Texas 79920–5001, USA

15–16 November 1991
Laparoscopic Cholecystectomy Workshop
Edinburgh, UK
Information: Mrs Maureen Webb, Royal College of Surgeons of Edinburgh, Nicolson Street, Edinburgh EH8 9DW, UK

17–23 November 1991
Surgery of the Pancreas, Liver and Biliary System
Edinburgh, UK
Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

19–22 November 1991
7th International Symposium on Cardio-pulmonary Urgencies and Emergencies
Rotterdam, The Netherlands
Information: Dr O. Prakash, University Hospital Rotterdam, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands

22 November 1991
Basic Surgical Training for SHOs and Registrars
Edinburgh, UK
Information: Mrs Maureen Webb, Royal College of Surgeons of Edinburgh, Nicolson Street, Edinburgh EH8 9DW, UK

25–29 November 1991
Specialist Short Course: Advanced Surgery/Urology for GPs
London, UK
Information: J. Ashton, Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

3–5 December 1991
6th International Workshop on Therapeutic Endoscopy
Hong Kong
Information: Dr J. W. C. Leung, Department of Medicine, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong

4–5 December 1991
Medical Lasers: Practice and Prospects
Glasgow, UK
Information: Dr N. Krasner, Secretary, British Medical Laser Association, Gastro-Intestinal Unit, Walton Hospital, Rice Lane, Liverpool L9 1AE, UK

12–13 December 1991
1st EEC Conference on Pain Research
Brussels, Belgium
Information: M. Staquet, Rue Heger-Bordet, 1, B-1000 Brussels, Belgium

13 December 1991
Section of Surgery of the Royal Society of Medicine Teaching Day
Sheffield, UK
Information: Postgraduate Centre, Northern General Hospital, Herries Road, Sheffield S5 7AU, UK

13 December 1991
12th Annual Study Day: The Role of the Plain Abdominal Radiograph in the Acute Abdomen
Canterbury, UK
Information: Postgraduate Administrator, Kent Postgraduate Medical Centre, Kent and Canterbury Hospital, Canterbury, Kent CT1 3NG, UK

5–8 January 1992
Postgraduate Gastroenterology Course
Oxford, UK
Information: Dr D. P. Jewell, Radcliffe Infirmary, Oxford OX2 6HE, UK

8 January–19 February 1992
Section A FRCS(Ed) Part-Time Revision Course
Edinburgh, UK
Information: Mrs Maureen Webb, Royal College of Surgeons of Edinburgh, Nicolson Street, Edinburgh EH8 9DW, UK

17–18 January 1992
Hong Kong Surgical Forum
Hong Kong
Information: Secretariat, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

17–19 January 1992
XXVIII Head and Neck Course
Liverpool, UK
Information: Mrs B. Cowley, Department of Otorhinolaryngology, University of Liverpool, Royal Liverpool Hospital, PO Box 147, Liverpool L69 3BX, UK

30 January 1992
'Graft Infection – The Hidden Problem'
London, UK
Information: Mr John Wolfe, Secretary, London Vascular Debating Group, St. Mary's Hospital, London W2 1NY, UK

27–28 February 1992
Surgical Masterclass on Endo-Anal Surgery for Consultant Surgeons
Edinburgh, UK
Information: Mrs Maureen Webb, Royal College of Surgeons of Edinburgh, Nicolson Street, Edinburgh EH8 9DW, UK

30 March–4 April 1992
Head and Neck Oncology: Current Issues and Recent Advances
London, UK
Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

1–3 April 1992
Association of Surgeons of Great Britain and Ireland Annual Meeting
Jersey, UK
Information: Ms Caroline Ross, The Royal College of Surgeons, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK

13–14 April 1992
Injury Research Group 1992 Meeting
Manchester, UK
Information: Dr R. N. Barton, North Western Injury Research Centre, Stopford Building, University of Manchester, Oxford Road, Manchester M13 9PT, UK

22–25 April 1992
Updating Course on Pancreatic Diseases
Genoa, Italy
Information: Organizing Secretariat, QB Service, Via Visconti Venosta 4, 21122 Milano, Italy

22–25 April 1992
2nd International Workshop and Symposium on Therapeutic Endoscopy and Gastroenterology
Shanghai, China
Information: Dr J. W. C. Yeung, Department of Medicine, Prince of Wales Hospital, Hong Kong

3–7 May 1992
7th International Congress on Senology (Breast Diseases) of the Senological International Society
Rhodes, Greece
Information: Congress Secretariat, 102 Michalakopoulou Street, GR-115 28 Athens, Greece

10–16 May 1992
Acute Trauma Management
Belfast, UK
Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

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